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ORIGINAL

September 11, 1992

Document Processing Center (TS-790)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)



88920010967

Dear Coordinator:

SECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/91 CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide" states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due process issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

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C E C A P



ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation's TSCA §8(e) reporting standard². This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.³ Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

²In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment. See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

³A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteria. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent⁴, the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- o the "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.⁵
- o the "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- o the "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.

⁴The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

⁵ See, e.g., 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). See also, Rollins Environmental Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determine whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

"a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified, See, 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 1978 "Statement of Interpretation/ Enforcement Policy",⁴³ Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide*.

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	} ⁶	} ⁷
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y ⁸
SKIN SENSITIZATION (ANIMALS)	N	Y ⁹
EYE IRRITATION	N	Y ¹⁰
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y ¹¹
REPRODUCTION STUDY	N	Y ¹²
DEVELOPMENTAL TOX	Y ¹³	Y ¹⁴

⁶43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporting of specific effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemical. Unknown effects occurring during such a range test may have to be reported if they are those of concern to the Agency and if the information meets the criteria set forth in Parts V and VII."

⁷Guide at pp.22, 29-31.

⁸Guide at pp.34-36.

⁹Guide at pp.34-36.

¹⁰Guide at pp.34-36.

¹¹Guide at pp.22; 36-37.

¹²Guide at pp.22

¹³43 Fed Reg at 11112

"Birth Defects" listed.

¹⁴Guide at pp.22

NEUROTOXICITY	N	Y ¹⁵
CARCINOGENICITY	Y ¹⁶	Y ¹⁷
MUTAGENICITY		
<i>In Vitro</i>	Y} ¹⁸	Y} ¹⁹
<i>In Vivo</i>	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Biocconcentration	Y} ²⁰	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reproducutive	N	N

¹⁵Guide at pp-23; 33-34.

¹⁶43 Fed Reg at 11112

"Cancer" listed

¹⁷Guide at pp-21.

¹⁸43 Fed Reg at 11112; 11115 at Comment 15

"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

¹⁹Guide at pp-23.

²⁰43 Fed Reg at 11112; 11115 at Comment 16.

75-43-4

CAS #~~593-70-4~~

Chem: Dichlorofluoromethane

Title: Ninety-day Inhalation Exposure of Rats and Dogs
to Vapors of Dichlorofluoromethane

Date: May 19, 1976

Summary of Effects: liver damage in rats.

NINETY-DAY INHALATION EXPOSURE OF RATS AND DOGS
TO VAPORS OF DICHLOROFUOROMETHANE (FC-21)

Haskell Laboratory Report No. 493-77

Medical Research Project No. 2222

SUMMARY

Rats and dogs were exposed to dichlorefluoromethane (FC-21) vapors at levels of 0, 0.1, and 0.5% (v/v) for six hours/day, five days/week, for 90 days.

During the study, excessive mortality and a moderate incidence of hair loss occurred in rats at both test levels. Rats at both test levels dying during the study, as well as those sacrificed at 45 and 90 days on test, showed gross and microscopic evidence of moderate to severe liver damage. Neither the mortality nor the histopathologic damage was proportional to the dosage.

Dogs exposed to 0.5% FC-21 showed a slight decrease in body weight during the study and only mild liver effects as evidenced by blood chemistry and histopathologic indices. No adverse effects were seen in dogs at 0.1% test level.

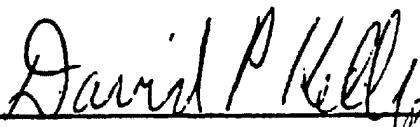
Both rats and dogs showed slight to moderate elevations in total urinary fluoride levels at 30, 60, and 90 days on test. In addition, no FC-21 was found in selected rat or dog tissues analyzed 18-36 hours after the last exposure.

**NINETY-DAY INHALATION EXPOSURE OF RATS AND DOGS
TO VAPORS OF DICHLOROFLUOROMETHANE (FC-21)**

Haskell Laboratory Report No. 493-77

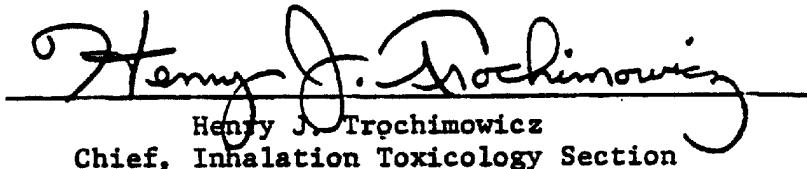
Medical Research Project No. 2222

Report by:



**David P. Kelly
Toxicologist**

Approved by:



**Henry J. Trochimowicz
Chief, Inhalation Toxicology Section**

The following reports are attached as appendices:

- A. Clinical Laboratory Report by John R. Barnes
Chief, Biochemistry Section
- B. Pathology Report by Taisan Chiu, D.V.M.
Senior Research Pathologist.

DPK:dhg:scg
Date Issued: July 8, 1977
N.B. E11616

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INTRODUCTION

Fluorocarbon 21 (FC-21, Dichlorofluoromethane) has a molecular weight of 102.9, a vapor pressure of 8.4 PSIG, and a boiling point of 8.9°C. Its major use is as a heat transfer liquid.

The inhalation toxicity of FC-21 has been investigated previously at Haskell Laboratory in several short-term experiments. The LC₅₀ for a single four-hour exposure in rats was shown to be 5.0% (v/v), thus indicating a low order of acute inhalation toxicity¹.

Cumulative effects were demonstrated in a two-week subacute inhalation study (10 rats, 6 hrs./day, 5 days/week, for two weeks) at 1.0% (v/v) in terms of biochemical and histopathological evidence of liver damage. Metabolism of FC-21 was suggested by increased total urinary fluoride levels (~ 5X control) in rats after the tenth exposure².

The purpose of this study was to evaluate the subchronic toxicity potential of FC-21.

METHODS

A. TEST MATERIAL

H. E. Phillips of Freon® Products Laboratory supplied cylinders containing about 150 pounds of FC-21. Each cylinder was analyzed by gas chromatography and contents found to be 99.9+% pure. Samples were assigned Haskell No. 9781.

B. ANIMALS

Groups of 54 ChR-CD rats (27/sex) and four pure-bred, male Beagle dogs were used at each test level. The rats were young adults at the start of the study. Female rats initially weighed between 134 and 217 grams; males weighed between 170 and 259 grams. The dogs were 10 to 12 months old and weighed 12.2 to 15.9 kg each. All test animals were allowed food and water ad libitum except during exposures. They were observed daily and weighed weekly during the exposure phase of the study.

C. VAPOR GENERATION AND ANALYSIS

Vapors from cylinders (heated to ~ 100° F) were metered into air streams supplying the chambers. Analysis of the chamber atmospheres was accomplished by drawing samples through stainless steel lines connecting the chambers to a microprocessor controlled gas chromatograph. By means of air operated stream selection and gas sampling valves, samples could be taken automatically at the desired time interval (every half-hour during exposure). The chromatograph was equipped with a flame ionization detector and an SE-30 column heated to 70°C. Peaks were integrated and concentrations calculated automatically, based on a calibration routine which was verified daily by manual injection of standard gas samples prepared in the laboratory.

D. EXPERIMENTAL DESIGN

Test animals were exposed to vapors of dichlorofluoromethane (FC-21) at levels of 0.1% or 0.5% in 1.4 m³ stainless steel chambers under dynamic exposure conditions. Exposures were conducted for six hours/day, five day/week over a 90-day period, during which the animals were observed, weighed, and clinically examined for adverse effects due to treatment. A group of control animals was handled in a similar manner but was exposed to air in a ventilated walk-in hood instead of a chamber.

During the study, histopathologic evaluations were performed on all rats dying or sacrificed in extremis, and on a randomly selected five rats/sex/level at 45 days. After 90 days, all the dogs and the remaining rats were autopsied. Animals were weighed weekly and these weights statistically analyzed after the study.

E. CLINICAL LABORATORY TESTS

Specimens of blood and urine from the Beagle dogs were examined on two occasions before the test began. This base-line data was used in assigning the dogs to test groups. No pretest samples were taken from rats.

At approximately monthly intervals during the study all of the dogs and 10 rats/sex/level were subjected to the following battery of clinical tests:

1. Hematology - measurements of red-cell count, hemoglobin, hematocrit, total and differential white-cell count.
2. Urinalysis - measurements of volume, osmolality, creatinine, pH, and fluoride ion concentration; tests for the presence of sugar, blood, acetone, bilirubin, and protein; and a microscopic examination of the sediment.

3. Blood Chemistry - measurements of alkaline phosphatase, glutamic-oxalacetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase, bilirubin, and total protein.

The following additional blood chemistry measurements were made on the dogs only: glucose, urea nitrogen, albumin/globulin, cholesterol, creatinine, and gamma-glutamyl transpeptidase.

FC-21 tissue analyses were performed on five rats and two dogs after 90 days exposure at the 0.5% level. Intervals of 18 hours (rats) and 72 hours (dogs) elapsed between the last exposure and the time of tissue collection. Body fat and adrenals were analyzed in rats; body fat alone in dogs. Methods are described in Haskell Report No. 469-76.

F. HISTOPATHOLOGIC EXAMINATION

At autopsy the major organs of all animals were weighed and examined grossly. All animals were then given a complete histopathologic examination except for the 0.1% level rats, in which case only the target organs were microscopically examined.

Complete histopathologic examination included brain*, pituitary*, eyes, trachea, lungs*, esophagus, stomach*, small and large intestines, liver*, gall bladder (dogs only), pancreas (*dogs only), thyroids and parathyroids (*dogs only), adrenals*, kidneys*, testes*, epididymides, prostate (*dogs only), bladder (*dogs only), salivary glands, lacrimal gland (rats only), heart*, aorta, lymph nodes, spleen*, thymus*, bone marrow, muscle, skin and mammary glands, ovaries and uterus. (* = organs weighed).

RESULTS

A. Chamber Monitoring

Chamber analyses over the 90-day test period resulted in average concentrations (\pm S.D.) of $0.10 \pm 0.01\%$ (v/v) and $0.49 \pm 0.04\%$, respectively, over the 90-day test period.

B. Clinical Observations and Body Weights Data

Rats were severely affected by exposure to FC-21 at both test levels. Deaths occurred after about 59 days on test and, by the end of the study, 20 rats from the 0.1% level and 15 rats from the 0.5% level had died (Fig. 1). The only apparent symptoms were a general weakness. Body weights appeared normal (Fig. 2) and the 0.5% level female rats showed an increased weight gain compared to controls.

We also observed a hair loss in some rats three weeks into the study. By the end of the 90 days, eight rats from the 0.1% level and 15 rats from the 0.5% level showed this effect. Males and females were affected similarly with some rats losing up to 50% of their coat.

Deaths occurred equally in rats with and without the hair loss. The mechanism for this hair loss was not determined. Some possible causes include hormonal changes, interference with keratinization, anti-mitotic activity, and local irritation. Pathologist K. P. Lee discusses these and other mechanisms of hair loss in a 1975 Haskell Laboratory report³.

Mortality and hair loss data are shown in tabular form in Table I.

Other than a slight statistically significant weekly weight loss at 0.5% level (Fig. 3) over the 90-day test period, dogs showed no adverse clinical effects from exposure to FC-21.

C. Clinical Chemistry

Dogs exposed to 0.5% Fluorocarbon 21 excreted a larger amount of fluoride than the untreated controls and had elevated plasma alkaline phosphatase, GOT, and LDH activities.

Rats from both the 0.1% and the 0.5% levels showed similar changes in fluoride excretion and plasma enzyme activity. These animals also showed a slight depression in the erythrocytes and total protein, an increase in the leucocytes in the peripheral blood, and excretion of a less concentrated urine.

The preceding increased enzyme activity is often associated with liver injury; the dilute urine observed in the rats with altered kidney function. The increased fluoride excretion in both rats and dogs suggests metabolic breakdown of the fluorocarbon with the release of inorganic fluoride.

No FC-21 was found in the tissues of rats sacrificed 18 hours after the last exposure or in dogs sacrificed 72 hours after the last exposure.

A detailed clinical laboratory report is given in the Appendix.

D. Histopathologic Examinations

Rats exposed to FC-21 had moderate to severe liver damage. Effects were similar at both test levels and appeared to be more severe in the females. Dogs received relatively minor effects from exposure and only at the 0.5% level.

Similar effects were seen in test rats at the 45- and 90-day sacrifices, and in those dying as a result of treatment between 45 and 90 days. Gross examination showed enlarged livers, spleens, and lymph nodes. Microscopically, there was post-necrotic fibrosis in the liver, increased hemopoiesis in the bone marrow and spleen, hemosiderin deposition and lymphocytic depletion in the lymph nodes, and nephrosis in the kidneys. The liver was considered the main target organ.

Additional changes were seen in rats at the 90-day sacrifice and in those dying between 45 and 90 days. These effects were considered to be secondary to the liver damage and include anemia, edema, heart failure cells in the lungs, pancreatic atrophy, and cytoplasmic vacuoles in the cells of the zona glomerulosa of the adrenal.

Dogs exposed to FC-21 at the 0.5% level showed changes in the liver characterized by a clumping of basophilic cytoplasmic material and nuclei of the hepatocytes. Dogs exposed at the 0.1% level showed no compound-related effect relative to histopathologic indices.

A detailed report on histopathologic evaluations is given in the Appendix.

TABLE I

Mortality and Hair Loss in Rats
Exposed to FC-21 for 90 Days

	0.1% Level		0.5% Level	
	Males	Females	Males	Females
Deaths*	8	12	10	5
Hair Loss	6	2	6	10

* All deaths occurred between 59 and 90 days on test.

RAT MORTALITY DURING 90-DAY INHALATION
TOXICITY STUDY ON FLUOROCARBON 21

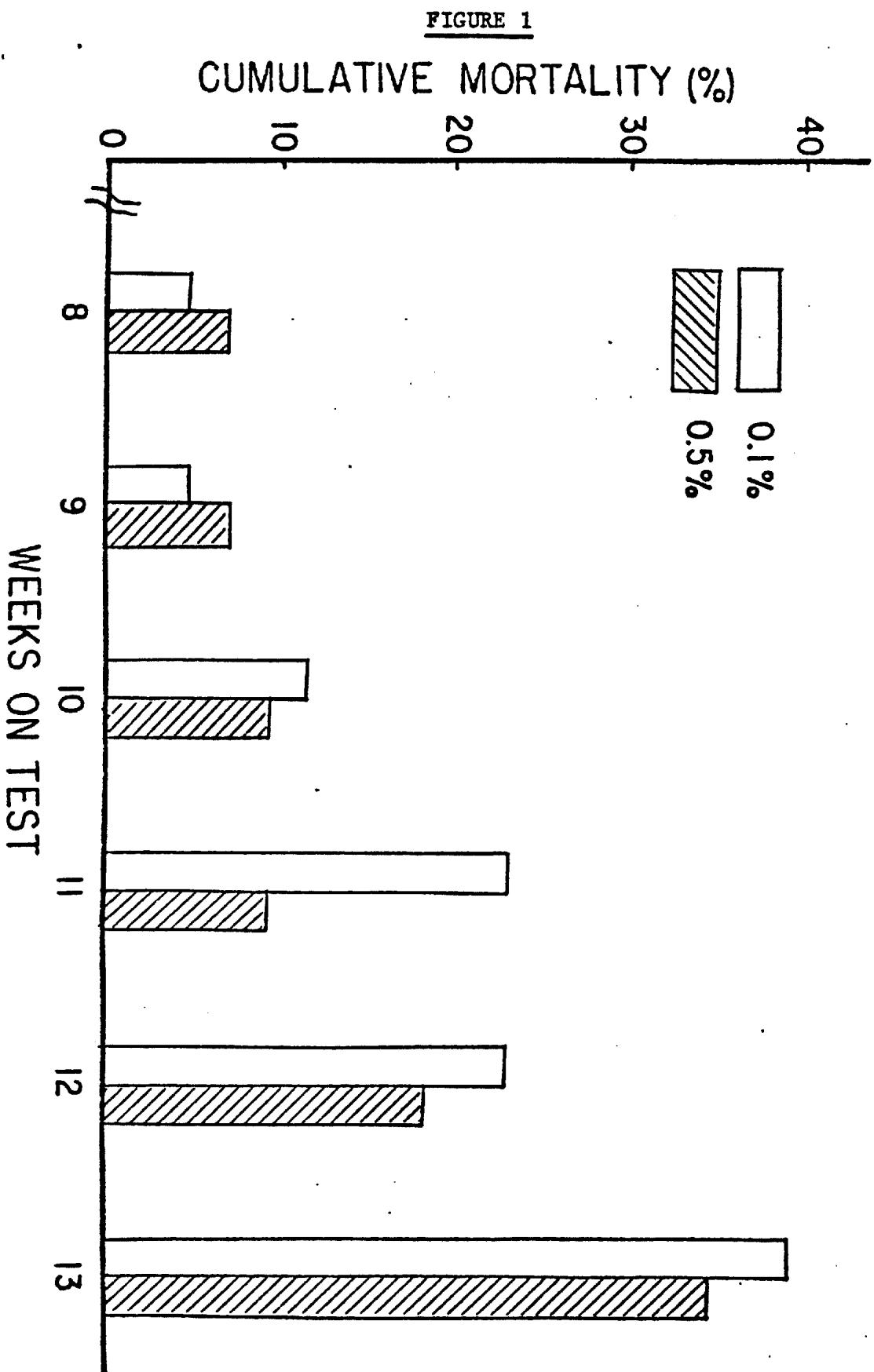
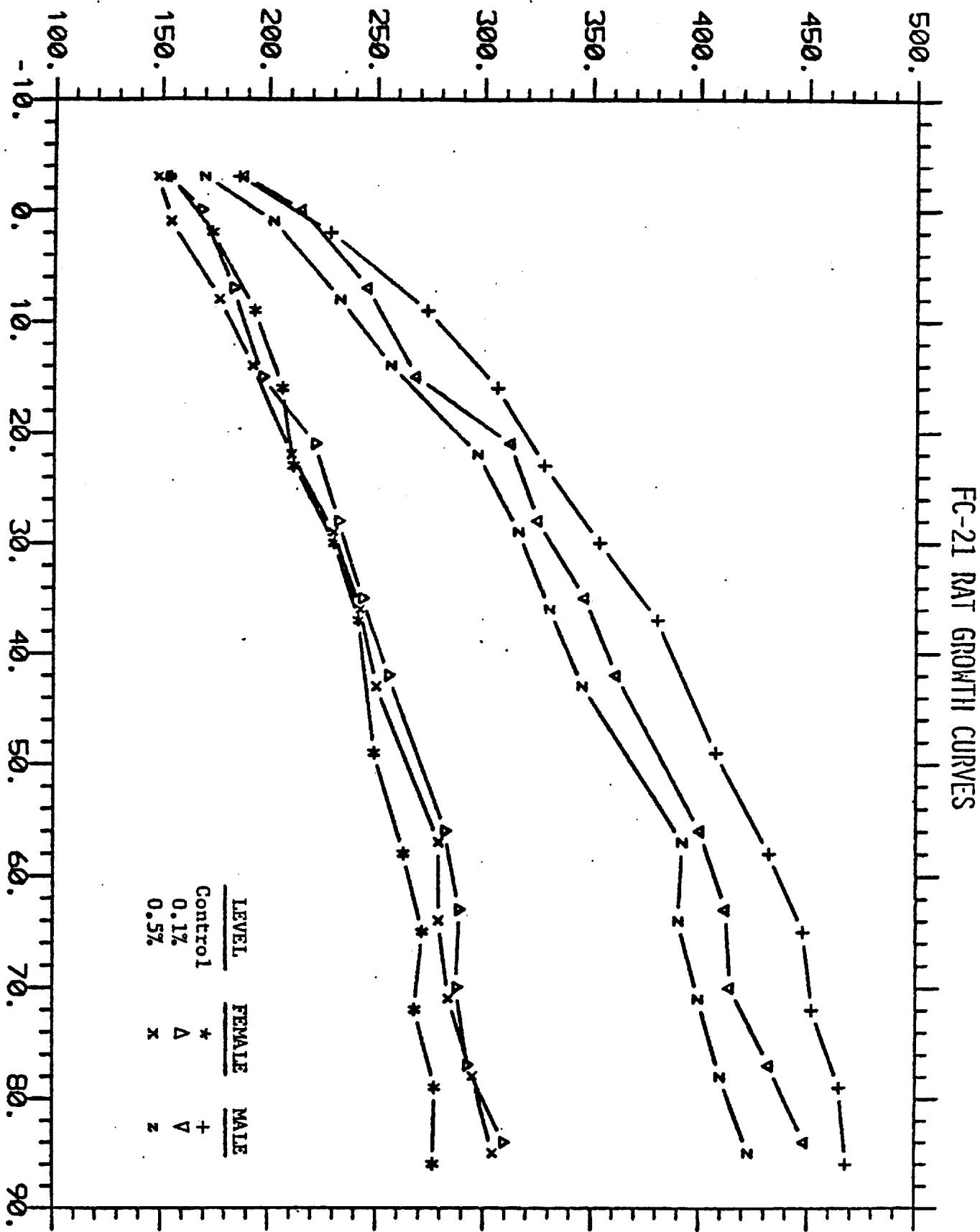


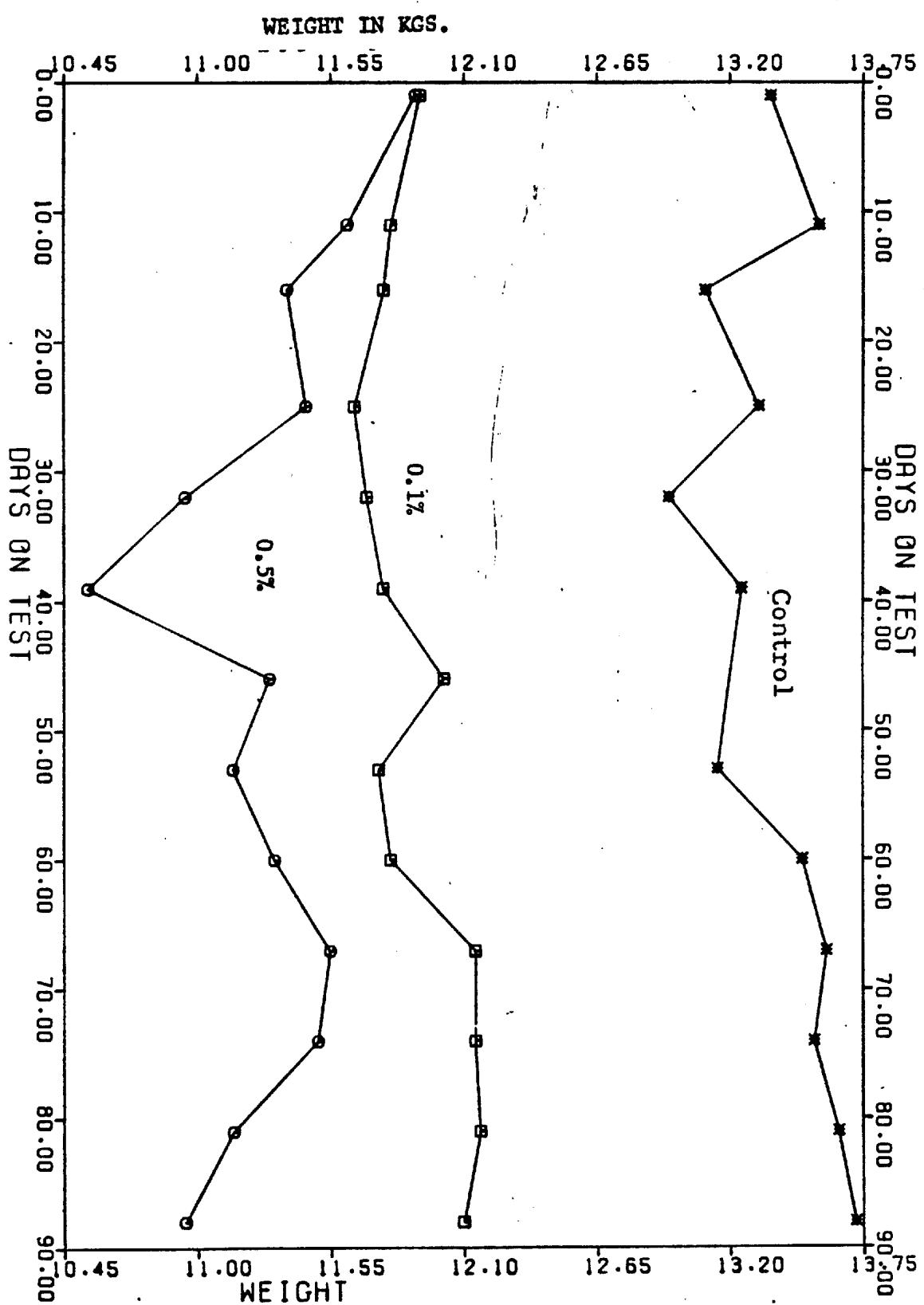
FIGURE 2
WEIGHT IN GRAMS



四

MR 2222 FC-21 DOG GROWTH CURVES

FIGURE 3



Bibliography

1. Acute Inhalation Toxicity, Haskell Laboratory Report No. 128-64.
2. Two-Week Inhalation Toxicity Studies, Haskell Laboratory Report No. 149-76.
3. Ninety-Day Inhalation Exposure of Dogs and Rats to Heated 1,2-Epoxy-3-Phenoxypropane, Haskell Laboratory Report No. 135-75.

APPENDIX A

TOXICOLOGICAL TESTING PROGRAM FOR ALTERNATE FLUOROCARBONS

FLUOROCARBON 21

Medical Research Project No. 2222

Haskell Laboratory No. 9781

CLINICAL LABORATORY REPORT

I. DOGS

Specimens of blood and 24-hour urine samples from twelve male Beagle dogs were examined on two occasions before the test began. The dogs were divided into three groups, one to serve as controls and the others to be exposed to 0.1% or 0.5% Fluorocarbon 21. At approximately monthly intervals after the exposures began the examinations were repeated on specimens of blood and overnight (16 hour) collections of urine.

The data were analyzed by partially nested and crossed analysis of variance and LSD tests, comparing treated groups with the control when the ratio of variances indicated an effect due to treatment. Significance was judged at the 0.5 probability level.

1. Hematology:

The hematologic examination of the blood consisted of a measure of the erythrocyte count, hemoglobin, hematocrit, total and differential leucocyte count.

The results of these examinations are summarized in the attached tables. No effect was observed in the exposed dogs that could be attributed to Fluorocarbon 21.

2. Urinalysis:

The examination of the urine consisted of a measure of the volume, concentration in milliosmoles, creatinine, a test for sugar, blood, acetone, bilirubin and protein and a microscopic examination of the sediment. The fluoride concentration in the urine and the total fluoride excreted during the sampling interval were measured after one and three months.

The results of the urinalysis are summarized in the attached tables. Increased amounts of fluoride were excreted by the dogs exposed to 0.5% Fluorocarbon 21. Other observations and measurements in the urine of the dogs exposed to Fluorocarbon 21 did not differ from the controls.

3. Clinical Chemistry:

The clinical chemistry measurements included glucose, urea nitrogen, alkaline phosphatase, glutamic-pyruvic transaminase (GPT), glutamic-oxalacetic transaminase (GOT), lactic dehydrogenase (LDH), gamma-glutamyltranspeptidase (γ -GTP), bilirubin, total protein, albumin/globulin, cholesterol and creatinine.

The results of these measurements are summarized in the attached tables. The dogs exposed to 0.5% Fluorocarbon 21 had elevated alkaline phosphatase, GOT and LDH activities. All other clinical chemistry measurements made on the dogs exposed to Fluorocarbon 21 did not differ from the controls.

II. RATS

1. Hematology:

Blood was taken from the tail of ten male and ten female rats in each group at approximately monthly intervals after the animals had been exposed to Fluorocarbon 21. The hematologic examination consisted of a measure of the erythrocyte count, hemoglobin, hematocrit, total and differential leucocyte count.

The results of these examinations are summarized in the attached tables. A small decrease was found in the hemoglobin of males and females and in the erythrocyte count and hematocrit of males exposed to 0.1% and 0.5% Fluorocarbon 21. An increase in the total leucocyte count, probably due to an increase in neutrophilic granulocytes, was also seen in both males and females.

2. Urinalysis:

An overnight (16 hour) sample of urine was collected from each of the rats subjected to the hematologic examination. The examination of the urine included a measure of the volume concentration in milliosmoles and pH; a test for sugar, blood, acetone, bilirubin and protein; a microscopic examination of the sediment from pooled specimens; the total amount of fluoride in the specimen and the amount per ml of urine.

The results of the urinalysis are summarized in the attached tables. Both male and female rats exposed to Fluorocarbon 21 excreted a larger volume of more dilute urine and larger amounts of fluoride than the controls.

3. Clinical Chemistry:

Blood was taken from the tails of ten male and ten female rats in each group at approximately monthly intervals to measure alkaline phosphatase, GOT, GPT and LDH activity and the bilirubin and total protein concentration.

The results of these measurements are summarized in the attached tables. The alkaline phosphatase, GOT and GPT activities in the plasma were increased and the total protein decreased in the rats exposed to Fluorocarbon 21.

III. SUMMARY

Dogs exposed to 0.5% Fluorocarbon 21 excreted a larger amount of fluoride than the untreated controls and had elevated plasma alkaline phosphatase, GOT and LDH activities.

Rats exposed to 0.1% as well as 5% Fluorocarbon 21 showed similar changes in fluoride excretion and plasma enzyme activity. These animals also showed a slight depression in the erythrocytes and total protein and increase in the leucocytes in the peripheral blood and the excretion of a less concentrated urine.

The increased enzyme activity is often associated with liver injury; the dilute urine observed in the rats with altered kidney function. The increased fluoride excretion in both rats and dogs suggests possible metabolic breakdown of the fluorocarbon with the release of inorganic fluoride.

The data are recorded in Biochemistry Section Notebooks E-5663, E-11627 and E-11628 and in the computer print-out filed with the Clinical Laboratory Report for the dogs and rats exposed to Fluorocarbon 142B under MR-2222-02.

Report by:

John R. Barnes

John R. Barnes
Chief, Biochemistry Section

JRB:ms

Date: May 19, 1976

SUMMARY OF URINALYSIS DATA ON DOGS EXPOSED TO FLUOROCARBON 21 FOR THREE MONTHS

	% FC in air	Pre-Test		Months on Test		
		1	2	3		
Volume ml		0	362	342	172	340
		0.1	221	330	158	239
		0.5	252	316	172	269
Osmolality mO _s		0	996	678	1236	854
		0.1	1400	982	1549	1360
		0.5	1270	1051	1107	1075
Creatinine mg/100 ml		0	72	52	123	67
		0.1	97	73	133	93
		0.5	88	82	97	76
Sugar number abnormal		0	0	0	0	0
		0.1	0	0	0	0
		0.5	0	0	0	0
Blood number positive		0	1	1	0	0
		0.1	0	1	0	0
		0.5	1	0	0	0
Acetone number positive		0	0	0	0	0
		0.1	0	0	0	0
		0.5	0	0	0	0
Bilirubin number positive		0	3	4	4	4
		0.1	4	4	4	4
		0.5	4	4	4	4
Protein number abnormal		0	0	0	0	0
		0.1	0	0	0	0
		0.5	0	0	1	0
Erythrocytes per hpf		0	0-2	0-1	0	0
		0.1	0	0-2	0	0-1
		0.5	0-3	0	0	0-1

SUMMARY OF URINALYSIS DATA ON DOGS EXPOSED TO FLUOROCARBON 21 FOR THREE MONTHS

	% FC in air	Pre-Test	Months on Test		
			1	2	3
Leuccocytes per hpf	0 0.1 0.5	0-2 0-2 0-3	0-2 0-1 0-2	0-3 0-3 0-2	0-1 0-2 0-3
Epithelial Cells per hpf	0 0.1 0.5	0-3 0-3 0-3	0-4 0-2 0-4	0-4 0-3 0-4	0-2 0-2 0-3
Bacteria	0 0.1 0.5	2+4+ 1+2+4+ 1+2+4+	3+4+ 2+4+ 3+4+	1+2+ 1+2+ 1+2+3+	1+2+ 1+2+4+ 1+
Casts per lpf	0 0.1 0.5	0 0 0	0 0 0	0 0 0	0 0 0
Fluoride μ g/ml	0 0.1 0.5		7.1 18.4 36.4		6.2 12.5 27.0
Fluoride μ/g	0 0.1 0.5		1675.6 2821.0 5809.3		1626.4 2842.3 8461.2

SUMMARY OF HEMATOLOGIC MEASUREMENTS ON DOGS EXPOSED TO FLUOROCARBON 21 FOR THREE MONTHS

	<u>% FC in Air</u>	Pre-Test	Months on Test		
			<u>1</u>	<u>2</u>	<u>3</u>
Erythrocytes $\times 10^6/\text{mm}^3$	0	6.10	6.30	6.20	6.51
	0.1	6.14	5.92	6.16	6.56
	0.5	6.00	6.14	6.20	6.41
Hemoglobin g %	0	15.7	15.9	15.8	15.9
	0.1	16.1	15.4	15.5	15.8
	0.5	15.3	15.6	15.7	15.5
Hematocrit %	0	45	45	46	47
	0.1	46	44	45	47
	0.5	44	45	45	46
Leucocytes $\times 10^3/\text{mm}^3$	0	12.9	17.6	13.0	14.2
	0.1	16.7	15.9	11.3	14.2
	0.5	12.6	14.2	8.2	10.9
Neutrophils %	0	57	55	54	56
	0.1	56	61	55	57
	0.5	58	58	54	58
Lymphocytes %	0	36	35	37	35
	0.1	38	33	38	34
	0.5	35	35	39	37
Eosinophils %	0	6.2	7.7	8.5	8.5
	0.1	5.3	6.3	6.0	6.5
	0.5	5.8	5.0	6.5	4.5
Monocytes %	0	1.0	1.8	1.3	0.8
	0.1	0.5	0.8	1.3	2.3
	0.5	0.5	1.3	0.8	0.8
Basophils %	0	0	0	0	0
	0.1	0	0	0	0
	0.5	0	0	0	0.3

SUMMARY OF CLINICAL CHEMISTRY MEASUREMENTS ON DOGS EXPOSED TO FLUOROCARBON 21 FOR THREE MONTHS

	% FC in Air	Pre-Test	1	Months on Test 2	3
Glucose mg %	0 0.1 0.5	106 111 107	101 105 105	104 104 104	105 105 102
Urea Nitrogen mg %	0 0.1 0.5	18 17 14	16 14 15	15 17 17	16 18 21
Alkaline Phosphatase BLB Units	0 0.1 0.5	2.1 2.3 2.0	2.3 2.1 2.0	1.8 2.4 3.5	2.0 2.4 3.4
GPT units	0 0.1 0.5	30 27 30	23 16 21	16 12 24	30 24 66
GOT units	0 0.1 0.5	18 12 15	18 18 19	19 16 18	8 7 11
LDH units	0 0.1 0.5	8 10 18	29 24 28	19 15 19	55 66 98
γ -GT units	0 0.1 0.5	2.0 1.9 1.6	1.9 1.4 1.7	4.7 4.0 5.0	2.8 2.9 5.6
Bilirubin mg %	0 0.1 0.5	0.2 0.2 0.2	0.2 0.2 0.2	0.2 0.2 0.3	0.3 0.2 0.3
Total Protein g %	0 0.1 0.5	6.6 6.7 6.5	6.5 6.4 6.4	6.6 6.4 6.6	6.0 6.0 6.3

SUMMARY OF CLINICAL CHEMISTRY MEASUREMENTS ON DOGS EXPOSED TO FLUOROCARBON 21 FOR THREE MONTHS

	% FC in Air	Pre-Test			Months on Test		
		1	2	3	1	2	3
Albumin/Globulin	0	1.03	0.85	1.08	1.22	1.02	
	0.1	0.87	1.03	1.20	1.21	1.04	
	0.5	0.87	0.95	1.01	1.08	1.06	
Cholesterol mg %	0	211	166	164	173	276	
	0.1	218	148	247	173	292	
	0.5	181	144	179	160	311	
Creatinine mg %	0	0.1	0.1	0.1	0.1	0.1	0.1
	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	0.5	0.1	0.1	0.1	0.1	0.1	0.1

SUMMARY OF URINALYSIS DATA ON RATS EXPOSED TO FLUOROCARBON 21 FOR THREE MONTHS

	% FC in Air	MALE			FEMALE		
		Months on Test			Months on Test		
		1	2	3	1	2	3
Volume ml	0	15	14	12	9	13	13
	0.1	32	47	24	54	60	46
	0.5	25	50	22	51	37	29
Osmolality mOs	0	1676	1770	1828	1563	1584	1378
	0.1	935	861	946	391	493	566
	0.5	1065	838	1260	465	726	842
Creatinine $\mu\text{g}/100 \text{ ml}$	0	66	-	84	53	-	46
	0.1	38	-	42	20	-	19
	0.5	42	-	53	21	-	28
Sugar number abnormal	0	0	0	0	0	0	0
	0.1	0	0	0	0	0	0
	0.5	0	0	0	0	0	0
Blood number positive	0	.1	1	3	1	1	0
	0.1	1	5	1	1	4	3
	0.5	1	2	3	2	2	2
Acetone number positive	0	0	0	0	0	0	0
	0.1	0	0	0	0	0	0
	0.5	0	0	0	0	0	0
Bilirubin number positive	0	10	10	0	2	3	0
	0.1	10	10	4	6	10	5
	0.5	10	10	2	7	10	4
Protein number abnormal	0	0	1	0	0	0	0
	0.1	0	0	2	0	0	0
	0.5	0	0	1	0	0	0

SUMMARY OF URINALYSIS DATA ON RATS EXPOSED TO FLUOROCARBON 21 FOR THREE MONTHS

	% FC in Air	MALE			FEMALE		
		Months on Test		1	Months on Test		2
		1	2		3	1	
Erythrocytes per hpf	0 0.1 0.5	0 ^a 0 ^a 0 ^a	0 ^a 0 ^e 0 ^b	0 ^c 0 ^a 0 ^c	0 ^a 0 ^a 0 ^b	0 ^a 0 ^d 0 ^b	0 ^c 0 ^b 0
Leucocytes per hpf	0 0.1 0.5	0-2 0-2 0-2	0-2 0-2 0-2	0-1 0-1 0-1	0-1 0-2 0-2	0-1 0-1 0-1	0-2 0 0-1
Epithelial Cells per hpf	0 0.1 0.5	0-5 0-6 0-3	0-1 1-2 0-2	0-1 0 0-1	0-2 0-10 0-3	0-1 0-2 0-2	0-2 0-2 0-2
Bacteria	0 0.1 0.5	1 ^t 1 ^t 2 ^t 1 ^t 2 ^t	1 ^t 1 ^t 1 ^t	3 ^t 3 ^t 2 ^t	1 ^t 1 ^t 2 ^t 1 ^t	1 ^t 1 ^t 1 ^t	3 ^t 2 ^t 3 ^t
Casts per hpf	0 0.1 0.5	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
Fluoride μg/ml	0 0.1 0.5	4.2 5.3 8.9	6.2 11.9 13.7	4.6 13.7 15.0	3.6 3.0 3.6	4.7 5.0 9.7	3.6 8.9 8.5
Fluoride μg	0 0.1 0.5	43.4 159.1 180.1	81.7 448.7 431.1	52.0 279.8 280.7	30.2 147.0 155.8	57.9 266.4 312.9	44.0 223.7 227.5

a - 1 out of 10
 a¹ - 1 out of 10 with hematuria
 b¹ - 2 out of 10/1 with hematuria
 c - 3 out of 10 with hematuria
 d - 4 out of 10/2 with hematuria
 e - 5 out of 10/4 with hematuria

SUMMARY OF HEMATOLOGIC MEASUREMENTS ON RATS EXPOSED TO FLUOROCARBON 21 FOR THREE MONTHS

	% FC in Air	MALE			FEMALE		
		Months on Test		1	Months on Test		1
		1	2		3	2	
Erythrocytes x 10 ⁶ /mm ³	0	6.72	6.75	6.56	6.22	6.57	5.87
	0.1	6.59	6.42	4.35	6.42	6.12	4.38
	0.5	6.54	5.97	4.03	6.40	6.21	4.48
Hemoglobin g %	0	15.5	15.2	15.6	15.0	14.5	14.9
	0.1	14.9	14.3	10.7	15.7	13.8	11.3
	0.5	15.2	13.5	10.1	15.5	14.2	11.7
Hematocrit %	0	51	49	52	46	46	47
	0.1	48	45	34	50	44	37
	0.5	48	44	32	51	45	37
Leucocytes x 10 ³ /mm ³	0	22.9	19.7	18.1	17.6	13.4	15.0
	0.1	25.3	33.1	38.0	27.4	25.7	26.6
	0.5	26.4	32.1	26.9	24.2	24.4	24.8
Neutrophils %	0	30	31	32	30	30	31
	0.1	32	32	33	35	29	33
	0.5	33	31	32	32	31	33
Lymphocytes %	0	64	62	64	62	64	63
	0.1	64	60	58	59	58	59
	0.5	62	61	62	63	60	58
Eosinophils %	0	5.0	6.6	4.4	6.2	6.0	6.1
	0.1	2.5	6.4	8.1	4.8	12.2	6.3
	0.5	4.0	6.7	5.4	5.2	8.8	7.7
Monocytes %	0	0.9	0.8	0.5	1.2	0.6	0.4
	0.1	1.4	1.1	1.2	1.1	1.2	1.5
	0.5	1.2	1.0	0.9	0.7	1.2	0.7
Basophils %	0	0	0	0	0	0	0
	0.1	0	0	0.2	0	0	0

SUMMARY OF CLINICAL CHEMISTRY MEASUREMENTS ON RATS EXPOSED TO FLUOROCARBON 21 FOR THREE MONTHS

	% FC in Air	MALE			FEMALE		
		Months on Test		3	Months on Test		3
		1	2		1	2	
Alkaline Phosphatase BLB units	0	23.5	16.0	16.6	15.6	12.7	10.2
	0.1	56.2	44.8	34.8	49.4	36.2	29.6
	0.5	61.7	46.1	41.8	49.3	48.4	41.8
GOT units	0	40	59	83	39	37	48
	0.1	512	646	138	315	582	580
	0.5	512	867	180	180	519	430
GPT units	0	30	45	44	37	50	53
	0.1	137	33	75	140	97	59
	0.5	137	74	90	129	44	70
LDH units	0	505	570	1033	994	803	1140
	0.1	456	548	529	817	469	404
	0.5	456	425	253	684	617	531
Bilirubin mg %	0	0.6	0.6	1.0	-	0.6	1.5
	0.1	0.8	0.9	0.6	-	1.3	1.0
	0.5	1.5	1.0	0.4	-	1.4	1.1
Total Protein g %	0	6.6	6.6	6.8	6.8	6.9	7.3
	0.1	6.2	5.9	5.4	6.5	6.0	6.2
	0.5	6.1	5.9	5.5	6.4	5.9	6.1

APPENDIX B

PATHOLOGY REPORT NO. 51-76

Dichlorofluoromethane (Freon® 21)

H-9781 - MR-2222 - Organic Chemicals Dept.

Ninety-Day Inhalation Exposure Study
ChR-CD Rats and Beagle Dogs

December 1, 1976

SUMMARY:

Under the experimental conditions of this study, Freon® 21 appeared to be hepatotoxic in the rat. There was no apparent dose-related response. However, there was a sex-related change. Female rats showed more prominent changes than males. The changes observed in various organs and tissues were considered to be the results of primary hepatic change.

In dogs, there was a mild change in the liver in the 0.5 percent level, whereas no apparent changes attributable to the exposure were noted at the 0.1 percent level.

RESULTS AND COMMENTS:

1. The pertinent animal identification, treatment schedule, gross and microscopic findings are presented in Tables I to VII. Only the gross lesions in rats considered to be exposure-related were listed. Common control groups were shared with Freon® 142b and are recorded in Pathology Report No. 27-76 (H-9786 - MR-2222) and not duplicated in this report.

After the tissues of the rats exposed to 0.5 percent Freon® 21 were evaluated microscopically, the liver was considered to be the target organ. Accordingly, only the livers of the 0.1 percent groups were examined microscopically. The results indicated that there was no apparent difference between the 0.5 percent and 0.1 percent groups.

2. Microscopic examination included brain*, pituitary*, eyes, trachea, lungs*, esophagus, stomach*, small and large intestines, liver*, gall bladder (dogs only), pancreas (*dogs only), thyroids and parathyroids (*dogs only), adrenals*, kidneys*, testes*, epididymides, prostate (*dogs only), bladder (* dogs only), salivary glands, lacrimal gland (rats only), heart*, aorta, lymph nodes, spleen*, thymus*, bone marrow, muscle, skin and mammary glands, ovaries and uterus. (* = organs weighed).

3. The test rats sacrificed at day 45 of the exposure period showed hepatomegaly, splenomegaly and enlarged lymph nodes. Alopecia was present in some rats. The microscopic examination revealed the feature of post-necrotic fibrosis in liver; increased hemopoiesis in the bone marrow and spleen; hemorrhage, hemosiderin deposition and lymphocytic depletion in

Note: Rat No. 193148 of the male control group was found to be a pregnant female at the time of necropsy. This rat was not included in this report.

lymph nodes; nephrosis in kidneys; and the reduction of hair shafts in the follicles.

4. Rats that died or were sacrificed after day 59 showed some changes similar to the alterations observed at day 45. In addition, other changes were observed. These changes were considered to be the results of the primary liver lesions. There was increased fibrosis and nodularity of the liver, anemia with increased hemopoiesis, edema, heart failure cells in the lungs, pancreatic atrophy, nephrosis and cytoplasmic vacuoles in the cells of the zona glomerulosa of the adrenal. Multiple thrombi were present in the mesenteric blood vessels of Rat No. 193103.

The hepatic changes appeared to be more prominent in the female rats than the males. There were no apparent dose or sex-dependent lesions detected in any other organs.

5. Alopecia was observed in varying degrees and location. The distribution appeared to be bilaterally symmetrical. The hair coat in these affected areas was sparse and shortened.

It should be noted that the microscopic examination of alopecia is extremely difficult due to the differences in the distribution and arrangement of the hair follicles, the variation in hair growth cycle, and the plane and level of the section prepared. A more extensive study would be needed to clarify this lesion.

6. Only livers of dogs exposed to 0.5 percent of the test compound were affected. There was a "clumping" of basophilic cytoplasmic material and nuclei of the hepatocytes.

7. The statistician's evaluation (Statistical Report No. 6-76) is appended to this report. Statistical analysis was done on the selected organs of animals sacrificed at day 45 and after day 79 of exposure. Animals that died during the exposure period were excluded.

Report by:

Taisan Chiu

Taisan Chiu, D.V.M.
Senior Research Pathologist

Approved by:

JGA/15111
James G. Aftosmis, D.V.M.
Manager, Pathology Section

TC:JGA:ljm

Date: December 1, 1976

SUMMARY OF MICROSCOPIC AND GROSS FINDINGS IN MALE BEAGLE DOGS EXPOSED TO FREON® 21 FOR THREE MONTHS

Dog No.	Dose %	LUNG		LIVER		Clumping of nucleic acid cytoplasmic contents
		Moderate change	Marked change	Moderate change	Marked change	
1525	0	2	1	-	-	-
1529	0	(1)	-	(1)	-	-
1530	0	-	-	-	-	-
1537	0	(1)	-	(1)	-	-
1531	0.5	1	-	-	1	-
1533	0.5	1	(1)	-	(1)	-
1535	0.5	-	(1)	-	-	-
1536	0.5	(1)	-	1	+	-
528	0.1	x	x	x	x	x
.538	0.1	x	x	x	x	x
541	0.1	x	x	x	x	x
543	0.1	x	x	x	x	x

Note: -x = Organ not examined or section not present on the slide. - = Change not present. + = Change present. 1 = Slight change. 2 = Moderate change. 3 = Marked change. (1) = Very slight change.

TABLE I (Continued)

SUMMARY OF MICROSCOPIC AND GROSS FINDINGS IN MALE BEAGLE DOGS EXPOSED TO FREON® 21 FOR THREE MONTHS

Part 2

Dog No.	KIDNEY	TESTIS	EPIDIDYMIS	PROSTATE	LYMPH NODES	THYMUS	SMALL INTESTINE	
							Focal calcification	Focal cyst
1525	0	(1)	-	1	1	(1)	1	-
1529	0	(1)	(1)	-	2	1	1	-
1530	0	(1)	(1)	-	1	3	1	1
1537	0	-	(1)	-	(1)	-	(1)	-
1531	0.5	(1)	-	1	(1)	2	-	-
1533	0.5	(1)	-	(1)	-	3	-	3
1535	0.5	(1)	-	-	-	-	1	-
1536	0.5	(1)	-	-	-	-	x	x
1528	0.1	x	x	x	x	x	x	x
1538	0.1	x	x	x	x	x	x	x
1541	0.1	x	x	x	x	x	x	x
1543	0.1	x	x	x	x	x	x	x

Code: x = Organ not examined or section not present on the slide. - = Change not present.
 (1) = Very slight change. 1 = Slight change. 2 = Moderate change. 3 = Marked change.

TABLE I (Continued)

SUMMARY OF MICROSCOPIC AND GROSS FINDINGS IN MALE BEAGLE DOGS EXPOSED TO FREON® 21 FOR THREE MONTHS

Dose μ	No.	Pancreas	Para-thyroid	Skin	Brain	Spinal Cord	Gross Findings	
							Focal fibrosis	Focal pale-stained nodule, actinarr cell infiltration
25	0	-	(1)	-	-	-	(1)	Several round worms in jejunum
29	0	-	-	-	-	-	(1)	No remarkable changes
30	0	-	-	(1)	-	-	-	Several blue nodules in left lung
37	0	(1)	(1)	-	-	-	-	Several grey-white nodules in left lung
31	0.5	-	-	-	-	-	-	No remarkable changes
533	0.5	-	-	-	-	-	-	No remarkable changes
535	0.5	-	-	-	-	-	-	Grey-white foci with dark spots in left diaphragmatic lobe
536	0.5	-	(1)	-	-	-	-	Few red nodules (0.1 and 0.3 cm) in left diaphragmatic lobe
528	0.1	x	x	x	x	x	x	Capsular fibrosis and few red foci in spleen; slight endocardiosis in right A-V valves
538	0.1	x	x	x	x	x	x	No remarkable changes
541	0.1	x	x	x	x	x	x	Raised nodules (0.3 cm) in lung; gray-white lesion on edge in both ends of spleen
543	0.1	x	x	x	x	x	x	Indentation at mid-portion of spleen

(1) = Very slight change. 1 = Slight change.

Code: x = Organ not examined or section not present on the slide. - = Change not present.

TABLE II

SUMMARY OF GROSS FINDINGS IN MALE RATS EXPOSED TO FREON® 21

GENERAL APPEARANCE	INTEG- IMENT	PLEURAL CAVITY	ABDOMINAL CAVITY	LIVER	SPLEEN	
					Capsular rupture	dark red, enlarged.
Days sacrificed or died (*)	Rat No.	Blood thin and pale	Anemic	Alopecia	Hydrothorax	Edematous mesentery/ omentum
	193028	0.1	45	-	-	-
	193029	0.1	45	-	-	-
	193052	0.1	45	-	-	-
	193053	0.1	45	-	-	-
	193054	0.1	45	-	-	-
	193104	0.5	45	-	-	-
	193105	0.5	45	-	-	-
	193106	0.5	45	-	-	-
	193107	0.5	45	-	-	-
	193108	0.5	45	-	-	-
	193043	0.1	70*	-	+	-
	193034	0.1	71*	-	-	-
	193040	0.1	77*	-	+	-
	193032	0.1	78*	-	+	-
	193033	0.1	93	-	-	-
	193051	0.1	93*	-	+	-
	193047	0.1	93*	-	-	+
	193042	0.1	94*	-	+	-

Code: * = Died. - = Change not observed.

Note: The changes considered to be treatment-related only are listed. Control group is not listed and is shared with Pathology Report No. 27-76 (H-9781-MR-2222).

Control group is not listed and is shared with

Part 2
TABLE II (Continued)SUMMARY OF GROSS FINDINGS IN MALE RATS EXPOSED TO FREQ^① 21

Rat No.	Days sacrificed or died (*)	Dose %	LYMPH NODES	KIDNEY	BONE MARROW	G.I. TRACT	TESTES	ADRENAL	Remarks
193028	0.1	45	-						Moderate post-mortem changes
193029	0.1	45	+						Moderate post-mortem changes
193052	0.1	45	+						Advanced post-mortem changes, no tissue
193053	0.1	45	+						Hair loss not observed at time of sacrifice
193054	0.1	45	+						Slight post-mortem changes
193104	0.5	45	+						
193105	0.5	45	+						
193106	0.5	45	-						
193107	0.5	45	+						
193108	0.5	45	+						
193043	0.1	70*	-						
193034	0.1	71*	-						
193040	0.1	77*	-						
193032	0.1	78*	-						
193033	0.1	93	-						
193051	0.1	93*	+						
193047	0.1	93*	+						
193042	0.1	94*	+						

Code: * = Died. - = Change not observed. + = Change observed.

Part 3

TABLE II (Continued)
SUMMARY OF GROSS FINDINGS IN MALE RATS EXPOSED TO PREO[®] 21

Rat No.	Dose %	Days sacrificed or died (*)	Alopexia	Adermia	Abasiteca	Hydrothorax	Edematous mesentery/ omentum	Abcites	Plate brown, course	Enlarged, heavy	Nodules	dark red, enlarged,	Spleen	Cesular grey patch		
															LIVER	SPIELEN
193030	0.1	95	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193031	0.1	95	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193035	0.1	95	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193041	0.1	95	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193044	0.1	95	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193045	0.1	95	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193049	0.1	95	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193036	0.1	96	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193037	0.1	96	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193038	0.1	96	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193039	0.1	96	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193046	0.1	96	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193048	0.1	96	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193050	0.1	96	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193093	0.5	61*	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193085	0.5	70*	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193101	0.5	85*	No gross examination done	-	-	-	-	-	-	-	-	-	-	-	-	-
193087	0.5	86	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Code: * = Died, - = Change not observed. + = Change observed.

TABLE II (Continued)

SUMMARY OF GROSS FINDINGS IN MALE RATS EXPOSED TO FREON® 21

Part 4

Bar No.	Dose %	Days sacrificed or died (*)	Lymph Nodes	Kidney	Bone Marrow	G. I. Tract	Testes	Adrenal	Large, heavy	Hemorrhage	Edema	Bloody contents	Pale	Red	Granular	Enlarged	Red	Enlarged	Pale	Red	Enlarged	Bloody contents	Hemorrhage	Edema	Large, heavy	Remarks	Hair loss not observed at time of sacri		
									LARGE, HEAVY												MILD								
193030	0.1	95							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193031	0.1	95							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193035	0.1	95							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193041	0.1	95							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193044	0.1	95							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193045	0.1	95							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193049	0.1	95							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193036	0.1	96							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193037	0.1	96							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193038	0.1	96							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193039	0.1	96							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193046	0.1	96							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193048	0.1	96							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193050	0.1	96							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
193093	0.5	61*							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Slight post-mortem changes
193085	0.5	70*							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Moderate post-mortem changes	
193101	0.5	85*							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Very advanced post-mortem changes	
193087	0.5	86							-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		

Code: * = Died. - = Change not observed. + = Change observed.

TABLE II (Continued)
SUMMARY OF GROSS FINDINGS IN MALE RATS EXPOSED TO FREON® 21

No.	Dose %	Days scattered or died (%)	Alopecia	Anemia	Thin and pale blood	GENERAL APPEARANCE	INTEG- IMENT	PIEGLAR CAVITY	ABDOMINAL CAVITY	LIVER	SPLEEN
100	0.5	86	-	-	-						
1083	0.5	93	-	-	-						
095	0.5	93*	-	-	-						
1098	0.5	93*	-	-	-						
1096	0.5	94*	-	-	-						
3097	0.5	94	-	-	-						
3082	0.5	94	-	-	-						
3084	0.5	94	-	-	-						
3086	0.5	94	-	-	-						
93088	0.5	94	-	-	-						
93089	0.5	94	-	-	-						
93090	0.5	94	-	-	-						
93091	0.5	94	-	-	-						
93092	0.5	94	-	-	-						
193094	0.5	94	-	-	-						
193099	0.5	94	-	-	-						
193102	0.5	94	-	-	-						
193103	0.5	94	-	-	-						

+ = Change observed.

- = Change not observed.

Code: * = Died.

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TABLE II (continued)

SUMMARY OF GROSS FINDINGS IN MALE RATS EXPOSED TO FREON® 21

Part 6

at No.	Dose % Days sacrificed or died (*)	Lymph Nodes	Kidney	Bone Marrow	G.I. Tract	Testes	Adrenal	Remarks			
								Large, heavy	Hemorrhage	Edema	Bloody contents
93100	0.5	86						-	+	-	-
93083	0.5	93	*					Slight post-mortem changes			
93095	0.5	93*						Moderate post-mortem changes			
93098	0.5	93*						Slight post-mortem changes			
93096	0.5	94*						Moderate post-mortem changes			
93097	0.5	94*									
93082	0.5	94									
193084	0.5	94									
193086	0.5	94									
193088	0.5	94									
193089	0.5	94									
193090	0.5	94									
193091	0.5	94									
193092	0.5	94									
193094	0.5	94									
193099	0.5	94									
193102	0.5	94									
193103	0.5	94									

Code: * = Died. - = Change not observed. + = Change observed.

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SUMMARY OF GROSS FINDINGS IN FEMALE RATS EXPOSED TO FREON® 21

FILE III

GENERAL APPEARANCE	PILEURAL CAVITY	ABDOMINAL CAVITY	LIVER	SPLEEN	GROSS FINDINGS										
					CUTS					TUMORS					
Rat No.	Dose %	Days sacrificed or died (*)	Anemic	Thrin and pale blood	Hydrotorax	Ascites	Edematous omentum/ mesentery	Pale brown, coarse	Enlarged, heavy	Nodular	Enlarged, dark	Gastric patch			
193005	0.1	45	+ + + + +	- - - - -	- - - - -	- + + + +	- - - - -	+ + + + +	+ + + + +	- - - - -	- + + + +	- - - - -			
193006	0.1	45	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193025	0.1	45	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193026	0.1	45	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193027	0.1	45	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193067	0.5	45	+ + + + +	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193068	0.5	45	+ + + + +	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193079	0.5	45	+ + + + +	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193080	0.5	45	+ + + + +	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193081	0.5	45	+ + + + +	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193007	0.1	59*	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193016	0.1	61*	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193001	0.1	71*	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
198011	0.1	78*	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193018	0.1	78*	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193013	0.1	79	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193021	0.1	92*	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			
193010	0.1	93	- - - - -	- - - - -	- - - - -	- + + + +	- - - - -	- + + + +	- + + + +	- - - - -	- + + + +	- - - - -			

Code: * = Died. - = Change not observed. + = Change observed.

Note: The changes considered to be treatment-related only are listed. Control group is not listed and shared with Pathology Report No. 27-76 (H-9781-MR-2222).

TABLE III (Continued)

SUMMARY OF GROSS FINDINGS IN FEMALE RATS EXPOSED TO FREON® 21

MR-22222

Rat No.	Dose %	Days sacrificed or killed (*)	Lymph Nodes			Kidney	Bone Marrow	Eye	Remarks
			Red	Enlarged	Pale	Enlarged, pale	Hemorrhage, postmortem		
193005	0.1	45	+	-	-	-	-	-	Slight post-mortem changes
193006	0.1	45	+	-	-	-	-	-	Advanced post-mortem changes
193025	0.1	45	+	-	-	-	-	-	Moderate post-mortem changes
193026	0.1	45	+	-	-	-	-	-	Advanced post-mortem changes
193027	0.1	45	+	-	-	-	-	-	Advanced post-mortem changes
193067	0.5	45	-	-	-	-	-	-	Slight post-mortem changes
193068	0.5	45	-	+	-	-	-	-	Advanced post-mortem changes
193079	0.5	45	-	+	-	-	-	-	Moderate post-mortem changes
193080	0.5	45	-	+	-	-	-	-	Advanced post-mortem changes
193081	0.5	45	-	+	-	-	-	-	Advanced post-mortem changes
193007	0.1	59*	-	-	-	-	-	-	Advanced post-mortem changes
193016	0.1	61*	+	-	-	-	-	-	Advanced post-mortem changes
193001	0.1	71*	-	-	-	-	-	-	Advanced post-mortem changes
193011	0.1	78*	+	-	-	-	-	-	Advanced post-mortem changes
193018	0.1	78*	-	-	-	-	-	+	Advanced post-mortem changes
193013	0.1	79	-	-	-	-	-	+	Advanced post-mortem changes
193021	0.1	92*	-	-	-	-	-	-	Advanced post-mortem changes
193010	0.1	93	+	-	-	-	-	-	Advanced post-mortem changes

Code: * = Died. - = Change not observed. + = Change observed.

TABLE I (Continued)

SUMMARY OF GROSS FINDINGS IN FEMALE RATS EXPOSED TO FREON® 21

GENERAL APPEARANCE	PLEURAL CAVITY	ABDOMINAL CAVITY	LIVER	SPLEEN	GROSS FINDINGS	
					Enlarged, dark	Grey patch
Dose %						
Days sacrificed or died (*)						
Rat No.						
193017	0.1	95	-	-	-	-
193002	0.1	95	-	-	-	-
193008	0.1	96	-	-	-	-
193019	0.1	96	-	-	-	-
193012	0.1	99*	-	-	-	-
193023	0.1	99*	-	-	-	-
193003	0.1	99	-	-	-	-
193004	0.1	99	-	-	-	-
193009	0.1	99	-	-	-	-
193014	0.1	99	-	-	-	-
193015	0.1	99	-	-	-	-
193020	0.1	99	-	-	-	-
193022	0.1	99	-	-	-	-
193024	0.1	99	-	-	-	-
193061	0.5	61*	Half of anterior portion of the body cannibalized-lungs, heart, liver missing	-	-	-
193064	0.5	61*	-	-	+	-
193056	0.5	85*	-	-	+	-
193063	0.5	93	-	-	+	-

Code: * = Died. - = Change not observed. + = Change observed.

SUMMARY OF GROSS FINDINGS IN FEMALE RATS EXPOSED TO FREON® 21

Rat No.	Days sacrificed or died (*)	Dose %	LYMPH NODES	KIDNEY	BONE MARROW	EYE	Pale	Enlarged, pale, Red	Enlarged	Enlarged, pale, Hemorrhage,	Postmortem	Remarks	
193017	0.1	93	+	+	-	-	-	-	-	-	-	-	
193002	0.1	95	+	+	+	+	+	+	-	-	-	-	
193008	0.1	96	+	+	+	+	+	+	-	-	-	-	
193019	0.1	96	-	-	-	-	-	-	-	-	-	-	
193012	0.1	99*	-	-	-	-	-	-	-	-	-	-	
193023	0.1	99*	-	-	-	-	-	-	-	-	-	-	
193003	0.1	99	+	+	+	+	+	+	-	-	-	-	
193004	0.1	99	+	+	+	+	+	+	-	-	-	-	
193009	0.1	99	+	+	+	+	+	+	-	-	-	-	
193014	0.1	99	+	+	+	+	+	+	-	-	-	-	
193015	0.1	99	+	+	+	+	+	+	-	-	-	-	
193020	0.1	99	+	+	+	+	+	+	-	-	-	-	
193022	0.1	99	+	+	+	+	+	+	-	-	-	-	
193024	0.1	99	+	+	+	+	+	+	-	-	-	-	
193061	0.5	61*	61*	61*	61*	61*	61*	61*	61*	61*	61*	61*	Very advanced post-mortem changes
193064	0.5	61*	+	+	+	+	+	+	+	+	+	+	Advanced post-mortem changes, partially cannibalized
193056	0.5	85*	-	-	-	-	-	-	-	-	-	-	Very advanced post-mortem changes
193063	0.5	93	+	+	+	+	+	+	+	+	+	+	

Code: * = Died, - = Change not observed.
+ = Change observed.

TABLE II (Continued)

SUMMARY OF GROSS FINDINGS IN FEMALE RATS EXPOSED TO FREON® 21

Rat No.	Dose %	Days sacrificed or died (*)	Alopecia	Anemic	Thick and pale blood	GENERAL APPEARANCE	PLEURAL CAVITY	ABDOMINAL CAVITY	LIVER	SPLEEN	Capsulairy	
							Hydrothorax	Ascites	Edematous omentum/mesentery	Pale brown, coarse	Enlarged, heavy	Nodular
193055	0.5	95*	-	-	-	-	-	-	-	-	-	-
193057	0.5	96	-	-	-	-	-	-	-	-	-	-
193058	0.5	96	-	-	-	-	-	-	-	-	-	-
193059	0.5	96	-	-	-	-	-	-	-	-	-	-
193060	0.5	96	-	-	-	-	-	-	-	-	-	-
193062	0.5	96	-	-	-	-	-	-	-	-	-	-
193065	0.5	96	-	-	-	-	-	-	-	-	-	-
193066	0.5	96	-	-	-	-	-	-	-	-	-	-
193069	0.5	96	-	-	-	-	-	-	-	-	-	-
193070	0.5	96	-	-	-	-	-	-	-	-	-	-
193071	0.5	96	-	-	-	-	-	-	-	-	-	-
193072	0.5	96	-	-	-	-	-	-	-	-	-	-
193073	0.5	96	-	-	-	-	-	-	-	-	-	-
193074	0.5	96	-	-	-	-	-	-	-	-	-	-
193075	0.5	96	-	-	-	-	-	-	-	-	-	-
193076	0.5	96	-	-	-	-	-	-	-	-	-	-
193077	0.5	96	-	-	-	-	-	-	-	-	-	-
193078	0.5	96	-	-	-	-	-	-	-	-	-	-

Code: * = Died. - = Change not observed.

+ = Change observed.

TABLE II (Continued)

SUMMARY OF GROSS FINDINGS IN FEMALE RATS EXPOSED TO FREON® 21

Rat No.	Dose α	Days sacrificed or died (*)	LYMPH NODES	KIDNEY	BONE MARROW	EYE	PALe	Red	Enlarged	Enlarged, pale	Hemorrhage, posterior	Slight post-mortem changes	Remarks
193055	0.5	95*	-	-	-	-	-	-	-	-	-	-	-
193057	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193058	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193059	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193060	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193062	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193065	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193066	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193069	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193070	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193071	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193072	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193073	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193074	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193075	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193076	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193077	0.5	96	-	-	-	-	-	-	-	-	-	-	-
193078	0.5	96	-	-	-	-	-	-	-	-	-	-	-

Code: * = Died, - = Change not observed. + = Change observed.

Hair loss not observed at time of sacrifice

TABLE IV

SUMMARY OF MICROSCOPIC FINDINGS OF 90-DAY INHALATION STUDY OF FREON® 21 ON MALE RATS SACRIFICED AT DAY 45

Code: x = Tissue not examined. - = Change not present. (1) = Very slight change. 1 = Slight change. 2 = Moderate change. 3 = Marked change.

TABLE IV (Continued)

SUMMARY OF MICROSCOPIC FINDINGS OF 90-DAY INHALATION STUDY OF FREON® 21 ON MALE RATS SACRIFICED AT DAY 45

Rat No.	LYMPH NODES			BONE MARROW			THYMUS			TESTIS			EPIDIDYMIS			PROSTATE			SKIN		
	Dose per cent	Hemorrhage	Deposits	Deposition of lymphocyte	Edema	Deposits	Hypertrophy	Poilets	Acute lympho-	Vacuolar, acinar	Cytotic infiltration	Poilets	Focal hypo-	Focal lymphocytic	Infiltration	Focal lymphocytic	Decreased	Hair shaft	Halitine plug		
193158	0	2	1																		
193159	0	-	-																		
193160	0	2	2																		
193161	0	-	-																		
193162	0	2	1																		
193164	0.5	2	2																		
193165	0.5	3	2																		
193166	0.5	2	2																		
193167	0.5	3	2																		
193168	0.5	3	3																		
193028	0.1	x	x																		
193029	0.1	x	x																		
193052	0.1	x	x																		
193053	0.1	x	x																		
193054	0.1	x	x																		

Code: x = Tissue not examined. - = Change not present. + = Change present. (1) = Very slight change.
 2 = Moderate change. 3 = Marked change.

1 = Slight change.

TABLE V

**SUMMARY OF MICROSCOPIC FINDINGS OF 90-DAY INHALATION
STUDY OF FREON® 21 ON FEMALE RATS SACRIFICED AT DAY 45**

Dose (percent)	Histochemical reaction	Submucosal lympho- cytic infiltration	Infectious lesions	Pneumonia	Lymphocytic cuffing	Focal hemorrhage	Hyaline crystal	Heart failure cell	Ulcer focus	Focal lymphocytic	Cirrhosis	Focal chronic glomerulonephritis	Globomerulonephritis	Focal mineral deposit	Infiltrative lesion	Focal lympho- cytic	Giant cell	Focal chro- nitis	Giant cell	Focal lympho- cytic	Infiltration	KIDNEY	HEART	
193131	0	2	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193132	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193133	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
193134	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
193135	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
193067	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193068	0.5	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193079	0.5	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193080	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193081	0.5	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193005	0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
193006	0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
193025	0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
193026	0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
193027	0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Code: x = Tissue not examined. - = Change not present. (1) = Very slight change. 1 = Slight change. 2 = Moderate change. 3 = Marked change.

TABLE V (Continued)

SUMMARY OF MICROSCOPIC FINDINGS OF 90-DAY INHALATION STUDY OF FREON® 21 ON FEMALE RATS SACRIFICED AT DAY 45

Dose (percent) Rat No.	LYMPH NODES		SPLEEN		THYMUS		BONE MARROW		PANCREAS		SALIVARY GLAND		ADRENAL		PITUITARY		BRAIN		UTERUS		SKIN		HYALINE PLATE		
	Hemosiderin depositc	Edema	Decreased eryt-	hemopoiesis	Infiltration	Hyperplasia	Hemorrhage	(1)	Poecil lymphocyte	Infiltration	Vacuolar cytoplasmic	Acropical module	Glycoplasma hyaline	Globule	Exocapsular nodule	Cyst	Meningitis,	choroid plexus	Dilatection	Decreased hair	Shafte				
193131 0	-	-	-	-	-	-	-	(1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193132 0	-	-	-	-	-	-	-	(1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193133 0	-	-	-	-	-	-	-	(1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193134 0	-	-	-	-	-	-	-	(1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193135 0	-	-	-	-	-	-	-	(1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193067 0.5	2	2	2	2	2	2	2	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193068 0.5	-	-	-	-	-	-	-	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3
193079 0.5	3	3	3	3	3	3	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193080 0.5	-	-	-	-	-	-	-	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1
193081 0.5	3	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193005 0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
193006 0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
193025 0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
193026 0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
193027 0.1	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Code: x = Tissue not examined. - = Change not present. + = Change present. (1) = Very slight change. 1 = Slight change.
 2 = Moderate change. 3 = Marked change.

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SUMMARY OF MICROSCOPIC FINDINGS IN MALE RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Organ	Post-mortem change	No. of tissues examined	Dose (percent)		Rat No.
			Control	Test	
TRACHEA	Mucosal eosinophilic infiltration	1	*	93*	193095
	Submucosal cyst	1	*	93*	193096
	Infiltration of dead	1	*	94*	193097
	Days sacrificed or died	2	*	94*	193098
	Mucosal eosinophilic infiltration	2	(1)	93*	193099
	Submucosal cyst	2	(1)	93*	193081
	Infiltration of dead	2	(1)	93*	193100
	Days sacrificed or died	2	(1)	86	193087
	Mucosal eosinophilic infiltration	1	*	86	193085
	Submucosal cyst	1	*	85*	193101
	Infiltration of dead	1	*	70*	193093
LUNG	Infiltration of dead	1	*	61*	
	Edema	1	*		
	Heart fatigued cell	1	*		
	Eosinophilic crystal	1	*		
	Focal vascularization	1	*		
	Intergalactation	1	*		
	Fibrinousputulence	2	*		
	Pneumonia	3	*		
KIDNEY	Citriosis	3	*		
	Focal lymphocytic infiltration	1	*		
	Lary hemopoiesis	1	*		
	Focal extramedullary	1	*		
	Hepatopathy	2	*		
HEART	Local lymphocytic infiltration	1	*		

Note! Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: * = Rat died and showed various degrees of post-mortem change in organs and tissues. - = Change not present. + = Slight change. 2 = Moderate changes. 3 = Marked change.

TABLE VI (Continued)

SUMMARY OF MICROSCOPIC FINDINGS IN MALE
RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Rat No.	Dose (percent) Days sacrificed or died	Hemorrhage	Hemosiderin deposit	Decreased lymphocyte	Lymphadenitis	Increased mast cell	Hypertrophy	Focal hemorrhage	Peritonitis	Necrosis of germinal cell	Necrosis of spermatogonies	Focal hyperplasia	Thymus	Testes	Epididymis	Prostate		Stomach		Focal mucosal	
																Spleen	Bone Marrow	Stomach	Esophagus	Stomach	Esophagus
193093	0.5 61*	3	3	1	2	-	-	-	-	3	-	-	-	-	-	2	1	1	1	1	1
193095	0.5 70*	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-
193101	0.5 85*	-	-	-	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-
193087	0.5 86	3	3	2	-	-	-	-	-	3	-	-	-	-	-	(1)	-	-	-	-	-
193100	0.5 86	3	3	1	-	-	-	-	-	3	-	-	-	-	-	(1)	-	-	-	-	-
193093	0.5 93	3	1	-	-	1	-	3	(1)	3	-	-	-	-	-	(1)	-	-	-	-	-
193095	0.5 93*	3	3	1	-	-	-	3	-	3	-	-	-	-	-	(1)	-	-	-	-	-
193098	0.5 93*	-	-	-	-	-	-	-	-	3	-	-	-	-	-	(1)	-	-	-	-	-
193096	0.5 94*	3	3	1	-	3	-	3	-	3	-	-	-	-	-	(1)	-	-	-	-	-
193097	0.5 94*	3	3	2	-	3	-	3	-	3	-	-	-	-	-	(1)	-	-	-	-	-
193082	0.5 94	3	3	2	-	3	(1)	3	(1)	3	-	-	-	-	-	(1)	-	-	-	-	-

Note: Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-22222).

Code: * = Rat died and showed various degrees of post-mortem change in organs and tissues. - = Change not present.
1 = Slight change. 2 = Moderate change. 3 = Marked change.

(1) = Very slight change.

Part 3
TABLE VI (Continued)

SUMMARY OF MICROSCOPIC FINDINGS IN MALE RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Rat No.	Dose (percent)	Days secreted or died	Protozoa (?)	Intestine	Mesenteric blood vessels	Pancreas	Lacrimal gland	SALIVARY GLAND	URINARY BLADDER	EYE	BRAIN	SPINAL CORD	Hemorrhage	Hemorrhage	Cortical module	Vacuolated zones	Gliomegaly	Thick muscle	Skin	Focal degeneration	Focal necrosis	
																				(1)	(1)	
193093	0.5	61*	-																			
193085	0.5	70*	-																			
193101	0.5	85*	-																			
193087	0.5	86	-																			
193100	0.5	86	-																			
193083	0.5	93	-																			
193095	0.5	93*	-																			
193098	0.5	93*	-																			
193096	0.5	94*	-																			
193097	0.5	94*	-																			
193082	0.5	94	-																			

Note: Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-22222).

Code: * = Rat died and showed various degrees of post-mortem change in organs and tissues. - = Change not present. + = Change present.
(1) = Very slight change. 1 = Slight change. 2 = Moderate change. 3 = Marked change.

TABLE VI (Continued)

SUMMARY OF MICROSCOPIC FINDINGS IN MALE
RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Dose (Percent)	Days sacrificed or died	Hepatocellular degeneration	Submucosal cyst	Submucosal lymphoid infiltration	Intercstitial pneumonia	Lymphocytic cuffing	Local hemorrhage	Edema	Heart failure cell	Endophthalmitic crystallization	Mineracalization	Fibrilloputulent pneumonia	Cithosis	Peculiar lymphocytosis	Peculiar extramedullary hemopoiesis	Lary hemopoiesis	Peculiar lymphocytes	Peculiar infiltration	Hyperplasia	KIDNEY	HEART	Part 4			
193084	0.5	94	(1)	2	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
193086	0.5	94	1	(1)	1	-	1	1	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
193088	0.5	94	1	-	(1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
193089	0.5	94	2	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
193090	0.5	94	2	-	-	1	2	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-		
193091	0.5	94	1	2	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
193092	0.5	94	2	(1)	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
193094	0.5	94	1	(1)	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
193102	0.5	94	3	-	1	(1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
193103	0.5	94	1	3	1	(1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		

Note: Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: - = Change not present. (1) = Very slight change. 1 = Slight change. 2 = Moderate change. 3 = Marked change.

Part 5

TABLE VI (Continued)

SUMMARY OF MICROSCOPIC FINDINGS IN MALE
RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Rat No.	Dose (percent)	Bleeding	Hemosiderin deposit	Decreased lymphocyte	Lymphadenitis	Increased mast cell	Increased hemopoiesis	Hypoplasia	Testes	Epididymis	Prostate	Stomach	
193084	0.5	24	-	-	-	-	-	1	-	-	-	-	Locular mucosal necrosis
193086	0.5	24	3	2	1	2	3	2	-	-	-	-	Submucosal edema
193088	0.5	24	3	3	1	1	1	1	-	-	-	-	Mucosal cyst
193099	0.5	24	3	3	1	2	2	1	-	-	-	-	Locular mucosal necrosis
193090	0.5	24	3	3	1	2	1	2	-	-	-	-	Locular mucosal necrosis
193091	0.5	24	3	3	1	2	1	2	-	-	-	-	Locular mucosal necrosis
193092	0.5	24	3	3	1	2	1	2	-	-	-	-	Locular mucosal necrosis
193094	0.5	24	3	3	1	2	1	2	-	-	-	-	Locular mucosal necrosis
193099	0.5	24	3	3	1	2	1	2	-	-	-	-	Locular mucosal necrosis
193102	0.5	24	3	3	1	2	1	2	-	-	-	-	Locular mucosal necrosis
193103	0.5	24	3	3	1	2	1	2	-	-	-	-	Locular mucosal necrosis

Note: Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: - = Change not present. (1) = Very slight change.

1 = Slight change. 2 = Moderate change. 3 = Marked change.

SUMMARY OF MICROSCOPIC FINDINGS IN MALE RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Note: Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: - = Change not present.

(1) = Very slight change. 1 = Slight change.

2 = Moderate changes. 3 = Marked change.

TABLE VII

SUMMARY OF MICROSCOPIC FINDINGS IN FEMALE RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

TRACHEA	Dose (percent)	Days sacrificed or died	Microscopic esophagitis	Infiltrative cystitis	Pneumonia	Lymphocytic cuffing	Focal hemorrhage	Edema	Focal vascular metaplasia	Endophytic cysts	Heart failure cell	Endophytic cysts	Focal calcification	Cystic calcification	Cirrhosis	Focal necrosis	Metaplastic cell	Dense cellular infiltration	Focal hemorrhage	Edema	Focal necrosis	Metaplastic cell	Dense cellular infiltration	Focal calcification	Cystic calcification	Cirrhosis	Focal extramedullary hemopoiesis	Glomerulonephritis	Focal mineralization	Hepatopathy	Kidney	LIVER		KIDNEY	
193061 (1)	0.5	61*																																	
193064 (2)	0.5	61*																																	
193056 (3)	0.5	85*																																	
193063	0.5	93	(1)																																
193055	0.5	95*	1	2																															
193057	0.5	96	2	1																															
193058	0.5	96	1	1																															
193059	0.5	96	1	1																															
193060	0.5	96	1	1																															
193062	0.5	96	1	1																															
193065	0.5	96	2	1																															

Note: (1) No tissue saved because of cannibalization and very advanced post-mortem changes.

(2) Advanced post-mortem changes. Tissues were not saved.

(3) No tissues saved due to very advanced post-mortem changes.

Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: * = Rat died and showed various degrees of post-mortem change in organs and tissues. - = Change not present. (1) = Very slight change.

1 = Slight change. 2 = Moderate change. 3 = Marked change.

TABLE VII (Concluded)

SUMMARY OF MICROSCOPIC FINDINGS IN FEMALE
RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Part 2

Dose (percent)	Days affected or deleted	Hepatocellular degeneration	Submucosal cysts	Gastric mucosal lympho- cytic infiltration	Trachea	Lung	Liver	Kidney	Nephropathy									
									1	2	3	4	5	6	7	8	9	10
193066	0.5	96	1	(1)	-	-	-	-	1	1	1	1	1	1	1	1	1	1
193069	0.5	96	1	(1)	-	-	-	-	1	1	1	1	1	1	1	1	1	1
193070	0.5	96	3	(1)	-	-	-	-	1	2	2	2	2	2	2	2	2	2
193071	0.5	96	1	(1)	-	-	-	-	1	1	1	1	1	1	1	1	1	1
193072	0.5	96	2	(1)	-	-	-	-	1	2	2	2	2	2	2	2	2	2
193073	0.5	96	(1)	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1
193074	0.5	96	1	(1)	-	-	-	-	1	1	1	1	1	1	1	1	1	1
193075	0.5	96	(1)	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1
193076	0.5	96	(1)	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1
193077	0.5	96	1	(1)	-	-	-	-	1	1	1	1	1	1	1	1	1	1
193078	0.5	96	2	(1)	-	-	-	-	1	1	1	1	1	1	1	1	1	1

Note: Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: - = Change not present. (1) = Very slight change. 1 = Slight change. 2 = Moderate change. 3 = Marked change.

TABLE VII (Continued)

SUMMARY OF MICROSCOPIC FINDINGS IN FEMALE
RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Rat No.	Days sacrificed or died	Dose (percent)	Focal lymphoretic-uilar infiltration	Hemorrhage	Hemosiderin deposit	Decreased lymphocyte	Erythropoagocytosis	Increased hemopoiesis	Peritoneitis	Hemorrhage	Hyperplasia	BONE MARROW	THYROID	SPLEEN	LYMPH NODES	HEART	Dilatation		Endometrial squamous		Metaplasia		Uterus	
																	UTERUS	ENDOMETRIAL SQUAMOUS	METAPLASIA	UTERUS				
193061 (1)	0.5	61*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193064 (2)	0.5	61*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193056 (3)	0.5	85*	(1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(1)	1	1	1	1	1	1
193063	0.5	93	(1)	3	2	1	1	1	1	1	1	1	1	1	1	1	1	(1)	1	1	1	1	1	1
193055	0.5	95*	(1)	3	2	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-	-	-	-
193057	0.5	96	-	3	2	1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-	-	-	-
193058	0.5	96	1	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193059	0.5	96	-	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193060	0.5	96	-	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193062	0.5	96	(1)	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
193065	0.5	96	-	3	3	-	-	-	-	-	-	-	-	-	-	-	3	1	1	1	1	1	1	1

Note: (1) No tissue saved because of cannibalization and very advanced post-mortem changes.

(2) Advanced post-mortem changes. Tissues were not saved.

(3) No tissues saved due to very advanced post-mortem changes.

Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: * = Rat died and showed various degrees of post-mortem change in organs and tissues. - = Change not present.

(1) = Very slight change. 1 = Slight change. 2 = Moderate change. 3 = Marked change.

TABLE VII continued)

SUMMARY OF MICROSCOPIC FINDINGS IN FEMALE
RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Rat No.	Dose (percent)	Days sacrificed or died	Focal lymphoreticular ulcer infiltration	HEART				LYMPH NODES				SPLEEN				THYMUS				BONE MARROW				HYPERPLASIA				DELIABILITATION				ENDOMETRIAL SQUAMOUS METAPLASIA			
				1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4				
193066	0.5	96	-	-	-	-	-	3	3	1	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
193069	0.5	96	-	-	-	-	-	3	3	1	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
193070	0.5	96	-	-	-	-	-	3	3	(1)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2				
193071	0.5	96	-	-	-	-	-	3	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
193072	0.5	96	-	-	-	-	-	3	3	2	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
193073	0.5	96	-	-	-	-	-	3	3	1	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
193074	0.5	96	-	-	-	-	-	3	3	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
193075	0.5	96	-	-	-	-	-	3	3	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
193076	0.5	96	-	-	-	-	-	3	3	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
193077	0.5	96	1	-	-	-	-	3	3	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
193078	0.5	96	(1)	-	-	-	-	3	3	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			

Note: Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: - = Change not present. (1) = Very slight change. 1 = Slight change. 2 = Moderate change. 3 = Marked change.

TABLE I (Continued)

SUMMARY OF MICROSCOPIC FINDINGS IN FEMALE
RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Rat No.	Dose (percent) Days sacrificed or died	OVARY	Follicular cyst		Focal mucosal cyst	Edema	Focal lymphocytic infiltration	Edema, atrophy duct hyperplasia	Focal fibrosis with duct hyperplasia	Edema, atrophy	LACRI- MAL GLAND	Vaccuolated foci glomerulosa	Basophilic globule	Cyst	Decreased heart shaft	SKIN	
			STOMACH	INTEST- INE													
193061 (1)	0.5	61*															
193064 (2)	0.5	61*															
193056 (3)	0.5	85*															
193063	0.5	93	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-
193055	0.5	95*	-	-	-	2	-	-	-	-	2	(1)	2	-	-	-	-
193057	0.5	96	-	-	-	1	-	-	-	-	-	(1)	1	-	-	-	-
193058	0.5	96	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-
193059	0.5	96	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-
193060	0.5	96	-	-	1	-	(1)	-	-	-	1	-	-	-	-	-	-
193062	0.5	96	-	-	1	-	(1)	-	-	-	-	-	-	-	-	-	-
193065	0.5	96	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-

Note: (1) No tissue saved because of cannibalization and very advanced post-mortem changes.

(2) Advanced post-mortem changes. Tissues were not saved.

(3) No tissues saved due to very advanced post-mortem changes.

Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: * = Rat died and shwed various degrees of post-mortem change in organs and tissues. - = Organ not present on the section. (1) = Very slight change. 1 = Slight change. 2 = Moderate change.

x = Organ not present on the section.

TABLE V-i (Continued)

Part 6

SUMMARY OF MICROSCOPIC FINDINGS IN FEMALE RATS EXPOSED TO FREON® 21 FOR THREE MONTHS

Rat No.	Dose (percent)	Days exposed or dieted	Atretic follicle	Pollicular cyst	Focal mucosal cyst	Edema	Focal lymphocytic infiltration	Edema, hypertrophy duct hyperplasia	Edema, atrophy	Focal fibrosis with duct hyperplasia	Focal lymphocytic infiltration	Edema	Focal fibrosis with hypertrophy	Focal lymphocytic infiltration	Edema	Vaccumated focus	Elongerules	Focal lymphocytic infiltration	Edema	Basophilic globule	Cyst	Decreased hair shaft	Skin	
193066	0.5	96	-	(1)	2	(1)	-	1	1	-	1	-	1	-	1	-	-	-	-	-	-	-	-	-
193069	0.5	96	-	-	2	1	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
193070	0.5	96	-	1	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
193071	0.5	96	-	(1)	1	-	-	-	1	-	1	-	-	-	-	-	(1)	(1)	-	-	-	-	-	-
193072	0.5	96	-	-	-	2	1	-	1	-	1	-	-	-	-	1	-	-	-	-	-	-	-	-
193073	0.5	96	-	(1)	1	1	-	1	1	-	1	-	1	-	1	-	-	-	-	-	-	-	-	-
193074	0.5	96	-	-	-	-	-	-	1	-	1	-	1	-	1	-	-	-	-	-	-	-	-	1
193075	0.5	96	-	-	-	-	-	1	1	-	1	-	1	-	1	-	-	-	-	-	-	-	-	1
193076	0.5	96	3	-	-	-	-	1	1	-	1	-	1	-	1	-	-	-	-	-	-	-	-	2
193077	0.5	96	-	-	-	(1)	-	1	-	-	1	-	1	-	1	-	(1)	-	-	-	-	-	-	-
193078	0.5	96	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1

Note: Control group is not listed and is shared with Pathology Report No. 27-76 (H-9786 - MR-2222).

Code: - = Change not present. (1) = Very slight change. 1 = Slight change. 2 = Moderate change.

3 = Marked change.



CENTRAL RESEARCH AND DEVELOPMENT DEPT.
HASKELL LABORATORY

cc: N. D. Krivanek
H. J. Trochimowicz

October 11, 1976

TO: T. Chiu

FROM: W. E. Fayerweather

WECF

STATISTICAL ANALYSIS OF ORGAN AND BODY WEIGHTS OF MALE BEAGLE DOGS AND
MALE AND FEMALE RATS EXPOSED TO FREON® 21

MR-2222 H-9781

STATISTICAL REPORT NO. 6-76

One factor analysis of variance and least significant difference tests ($p < 0.05$) were employed in the analysis of the data. The results of the analyses are summarized in the attached tables. Low (0.1%) and high (0.5%) groups were in each case compared with concurrent controls.

Male beagles sacrificed after three months' exposure (tables 1&2)

Final body weight was significantly lower in the low and high exposure group. Relative liver weight was significantly higher in the high exposure group.

Male rats sacrificed at day 45 (tables 3&4)

Final body weight was significantly lower in the high exposure group. Relative and absolute spleen weights were significantly higher in the high exposure group; absolute spleen weight was also significantly higher in the low exposure group.

Relative kidney weight was significantly higher in the low and high exposure group; absolute kidney weight was also significantly higher in the low exposure group.

October 11, 1976

Female rats sacrificed at day 45 (tables 5&6)

Final body weight was significantly higher in the low exposure group. Absolute liver weight was significantly higher in the low and high exposure groups; relative liver weight was also significantly higher in the low exposure group. Absolute spleen weight was significantly higher in the low and high exposure groups. Absolute kidney weight was significantly higher in the low exposure group.

Male rats sacrificed at day 90 (tables 7&8)

Initial body weight was significantly lower in the high exposure group. Final body weight was significantly lower in the low and high exposure group. Relative and absolute spleen and kidney weights were significantly higher in the low and high exposure groups.

Relative adrenal and heart weights were significantly higher in the low and high exposure groups; absolute adrenal and heart weight were also significantly higher in the low exposure group.

Female rats sacrificed at day 90 (tables 9&10)

Relative and absolute liver, spleen, kidney, and heart weights were significantly higher in the low and high exposure groups.

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STATISTICAL REPORT NO. 6-76

TABLE 1

MEAN BODY WEIGHTS (kg) AND ORGAN WEIGHTS (gm) OF MALE BEAGLE DOGS
EXPOSED TO FREON® 21 FOR THREE MONTHS

<u>Group</u>	<u>Initial Body Weight</u>	<u>Final Body Weight</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Testes</u>	<u>Adrenals</u>
Control	14.8	13.9	448.4	35.7	69.6	24.8	1.74
Low (0.1%)	13.5	11.8(↓)	407.7	30.3	57.3	22.1	1.54
High (0.5%)	13.8	11.3(↓)	478.1	29.9	64.5	20.3	1.51
F(1) LSD(2)	1.6 1.7	7.6* 1.6	2.0 80.5	2.2 7.1	2.3 13.2	1.7 5.6	1.5 0.30

(1) Among group F statistic.

(2) Least significant difference--any two means differing by more than LSD are significantly different at the 0.05 probability level.

(↓) Significantly less than the control group at the 0.05 probability level.

* Significant at the 0.05 probability level.

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TABLE 2

RELATIVE ORGAN WEIGHTS (% BODY WEIGHT) OF MALE BEAGLE DOGS
EXPOSED TO FREON® 21 FOR THREE MONTHS

<u>Group</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Testes</u>	<u>Adrenals</u>
Control	3.23	0.256	0.499	0.178	0.013
Low (0.1%)	3.46	0.258	0.486	0.187	0.013
High (0.5%)	4.26(†)	0.264	0.571	0.179	0.013
F(1) LSD(2)	5.2* 0.78	0.1 0.051	3.2 0.084	0.2 0.035	0.01 0.004

- (1) Among group F statistic.
 (2) Least significant difference--any two means differing by more than the LSD are significantly different at the 0.05 probability level.
 (†) Significantly greater than the control group at the 0.05 probability level.
 * Significant at the 0.05 probability level.

TABLE 3

MEAN BODY WEIGHTS (gm) AND ORGAN WEIGHTS (gm) OF MALE RATS
EXPOSED TO FREON® 21 AND SACRIFICED AT DAY 45

<u>Group</u>	<u>Initial Body Weight</u>	<u>Final Body Weight</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Thymus</u>	<u>Testes</u>	<u>Adrenals</u>	<u>Heart</u>
Control	185.2	403.0	17.4	0.70	3.19	0.67	3.42	0.067	1.25
Low (0.1%)	193.6	370.0	20.8	1.35(†)	4.02(†)	0.59	3.21	0.068	1.22
High (0.5%)	173.2	335.2(‡)	18.4	1.22(†)	3.53	0.70	3.28	0.051	1.27
F(1) LSD(2)	2.7 19.5	3.5 56.8	2.5 3.5	8.6** 0.36	4.2* 0.63	0.4 0.28	0.6 0.42	0.7 0.036	0.0 0.37

(1) Among group F statistic.
(2) Least significant difference--any time two means differing by more than the LSD are significantly different at the 0.05 probability level.

(1) (‡) Significantly greater than (less than) the control group at the 0.05 probability level.
* Significant at the 0.05 probability level.
** Significant at the 0.01 probability level.

TABLE 4
RELATIVE ORGAN WEIGHTS (% BODY WEIGHT) OF MALE RATS
EXPOSED TO FREON® 21 AND SACRIFICED AT DAY 45

<u>Group</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Thymus</u>	<u>Testes</u>	<u>Adrenals</u>	<u>Heart</u>
Control	4.38	0.18	0.81	0.17	0.86	0.016	0.32
Low (0.1%)	5.70	0.37(↑)	1.10(↑)	0.16	0.88	0.019	0.34
High (0.5%)	5.55	0.37(↑)	1.07(↑)	0.21	0.98	0.015	0.38
F(1) LSD(2)	2.5 1.43	7.2** 0.13	3.6 0.26	1.1 0.09	1.3 0.18	0.2 0.010	0.6 0.14

(1) Among group F statistic.
(2) Least significant difference--any two means differing by more than the LSD are significantly different at the 0.05 probability level.

(↑) Significantly greater than the control group at the 0.05 probability level.

** Significant at the 0.01 probability level.

TABLE 5

MEAN BODY WEIGHTS (gm) AND ORGAN WEIGHTS (gm) OF FEMALE RATS
EXPOSED TO FREON® 21 AND SACRIFICED AT DAY 45

<u>Group</u>	<u>Initial Body Weight</u>	<u>Final Body Weight</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Thymus</u>	<u>Adrenals</u>	<u>Heart</u>
Control	157.0	224.4	10.8	0.57	2.06	0.58	0.078	0.86
Low (0.1%)	161.0	270.0(†)	17.6(†)	1.05(†)	2.89(†)	0.59	0.084	1.03
High (0.5%)	156.2	244.4	14.5(†)	1.06(†)	2.63	0.40	0.064	0.82
F(1)	0.5	1.1	10.8**	3.2	4.4*	1.4	1.7	2.1
LSD(2)	11.9	44.9	3.2	0.48	0.63	0.29	0.024	0.24

(1) Among group F statistic.

(2) Least significant difference--any two means differing by more than the LSD are significantly different at the 0.05 probability level.

(†) Significantly greater than the control group at the 0.05 probability level.

* Significant at the 0.05 probability level.
** Significant at the 0.01 probability level.

TABLE 6

RELATIVE ORGAN WEIGHTS (% BODY WEIGHT) OF FEMALE RATS
EXPOSED TO FREON® 21 AND SACRIFICED AT DAY 45

<u>Group</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Thymus</u>	<u>Adrenals</u>	<u>Heart</u>
Control	4.50	0.24	0.86	0.24	0.032	0.36
Low (0.1%)	6.62(†)	0.39	1.08	0.22	0.032	0.39
High (0.5%)	5.96	0.43	1.08	0.16	0.026	0.33
F(1)	4.7*	2.4	2.0	1.3	0.9	0.6
LSD(2)	1.55	0.21	0.29	0.12	0.011	0.11

- (1) Among group F statistic.
(2) Least significant difference--any two means differing by more than the LSD are significantly different at the 0.05 probability level.
(†) Significantly greater than the control group at the 0.05 probability level.
* Significant at the 0.05 probability level.

TABLE 7

**MEAN BODY WEIGHTS (gm) AND ORGAN WEIGHTS (gm) OF MALE RATS
EXPOSED FREON® 21 AND SACRIFICED AT DAY 90**

<u>Group</u>	<u>Initial Body Weight</u>	<u>Final Body Weight</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Testes</u>	<u>Adrenals</u>	<u>Heart</u>
Control	185.1	508.0	19.9	0.81	3.82	3.24	0.063	1.51
Low. (0.1%)	188.5	435.0(↓)	20.6	2.57(↑)	5.28(↑)	3.17	0.085(↑)	1.77(↑)
High (0.5%)	166.3(↓)	402.8(↓)	18.1	2.38(↑)	4.65(↑)	3.04	0.075	1.66
F(1)	8.7**	13.1**	1.4	23.1**	13.1**	0.4	4.6*	4.1*
LSD(2)	11.5	42.1	3.1	0.57	0.58	0.48	0.015	0.18

(1) Among group F statistic.
 (2) Least significant difference--any two means differing by more than LSD are significantly different at the 0.05 probability level.

(↑) (↓) Significantly greater than (less than) the control group at the 0.05 probability level.

* Significant at the 0.05 probability level.

** Significant at the 0.01 probability level.

TABLE 8

RELATIVE ORGAN WEIGHTS (% BODY WEIGHT) OF MALE RATS
EXPOSED TO FREON® 21 AND SACRIFICED AT DAY 90

<u>Group</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Testes</u>	<u>Adrenals</u>	<u>Heart</u>
Control	3.93	0.16	0.76	0.69	0.013	0.30
Low (0.1%)	4.79(†)	0.59(†)	1.22(†)	0.74	0.020(†)	0.41(†)
High (0.5%)	4.46	0.59(†)	1.15(†)	0.75	0.019(†)	0.41(†)
F(1)	3.7*	29.8**	50.0**	1.6	10.1**	38.3**
LSD(2)	0.64	0.14	0.10	0.07	0.004	0.03

- (1) Among group F statistic.
- (2) Least significant difference--any two means differing by more than the LSD are significantly different at the 0.05 probability level.
- (†) Significantly greater than the control group at the 0.05 probability level.
- * Significant at the 0.05 probability level.
- ** Significant at the 0.01 probability level.

TABLE 9
MEAN BODY WEIGHTS (gm) AND ORGAN WEIGHTS (gm) OF FEMALE RATS
EXPOSED TO FREON® 21 AND SACRIFICED AT DAY 90

<u>Group</u>	<u>Initial Body Weight</u>	<u>Final Body Weight</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Adrenals</u>	<u>Heart</u>
Control	154.2	291.7	11.2	0.59	2.22	0.078	1.00
Low (0.1%)	150.2	297.7	17.9(↑)	2.02(↑)	3.36(↑)	0.076	1.30(↑)
High (0.5%)	146.6	291.5	17.8(↑)	1.79(↑)	3.60(↑)	0.072	1.27(↑)
F(1) LSD(2)	1.5 9.8	0.1 27.2	16.5** 3.3	32.2** 0.42	49.4** 0.33	2.1 0.008	13.1** 0.14

(1) Among group F statistic.

(2) Least significant difference--any two means differing by more than the LSD are significantly different at the 0.05 probability level.

(↑) Significantly greater than the control group at the 0.05 probability level.

** Significant at the 0.01 probability level.

MR-2222

H-9781

STATISTICAL REPORT NO. 6-76

TABLE 10

RELATIVE ORGAN WEIGHTS (% BODY WEIGHT) OF FEMALE RATS
EXPOSED TO FREON® 21 AND SACRIFICED AT DAY 90

<u>Group</u>	<u>Liver</u>	<u>Spleen</u>	<u>Kidneys</u>	<u>Adrenals</u>	<u>Heart</u>
Control	3.83	0.20	0.77	0.028	0.35
Low (0.1%)	5.94(†)	0.69(†)	1.13(†)	0.026	0.44(†)
High (0.5%)	6.16(†)	0.62(†)	1.24(†)	0.025	0.44(†)
F(1)	20.4**	28.3**	84.0**	0.9	14.2**
LSD	0.90	0.15	0.09	0.004	0.04
LA					

(1) Among group F statistic.

(2) Least significant difference--any two means differing by more than the LSD are significantly different at the 0.05 probability level.

(†) Significantly greater than the control group at the 0.05 probability level.
** Significant at the 0.01 probability level.

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F

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4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
79 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> S 593-70-4/RN

L14 1 593-70-4/RN

=> DIS

L14 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1995 ACS
RN ***593-70-4*** REGISTRY
CN Methane, chlorofluoro- (6CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:

CN Chlorofluoromethane

CN FC 31

CN Fluorochloromethane

CN Freon 31

CN HCFC 31

CN Methylene chloride fluoride

CN R 31

CN R 31 (refrigerant)

ES CONCORD

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LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA,
CANCERLIT, CAOLD, CASREACT, CEN, CHEMINFORMRX, CHEMLIST, CIN,
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Dichlorofluoromethane
Gas# - 75-43-4
Don't know what
chemical Gas# 593-70-
is for 4

C1.....CH2.....F

281 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
79 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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L15 1 2615-25-0/RN

=> DIS

Triage of 8(e) Submissions

Date sent to triage: 2/5/96

NON-CAP

CAP

Submission number: 13164A

TSCA Inventory:

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Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

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SUBMITTER NAME: E. T. Direct de
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INFORMATION REQUESTED: F.W.P DATE:

NO INFO REQUESTED

ONE INFO REQUESTED (TECH)

ONE INFO REQUESTED (VNL ACTION)

ONE INFO REQUESTED (REPORTING RATIONALE)

ONE INFO REQUESTED (REPORTING RATIONALE)

ONE INFO REQUESTED (SCREENING)

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ONE INFO REQUESTED (DISCONTINUITY)

ONE INFO REQUESTED (DISCONTINUITY)

ONE INFO REQUESTED (CONFIDENTIAL)

ONE INFO REQUESTED (CONFIDENTIAL)

SUB. DATE: 09/11/92 ON DATE: 09/22/92 CIRCD DATE: 04/24/95

CHEMICAL NAME

Dichlorofluoromethane

Freon 21

INFORMATION TYPE	P.E.C.	INFORMATION TYPE	P.E.C.
ONCO (ANIMAL)	01 02 04	ONCO (HUMAN)	01 02 04
ONCO (ACCIDENTAL)	01 02 04	CHAMPSY PROP	01 02 04
HUMAN EXPOS (ACCIDENTAL)	01 02 04	CLASTO (IN VITRO)	01 02 04
HUMAN EXPOS (CONTINUOUS)	01 02 04	CLASTO (ANIMAL)	01 02 04
BIOLOGICAL TOX	01 02 04	CLASTO (HUMAN)	01 02 04
SAR, OXOCO, FAAT	01 02 04	DNA DAMAGE/REP	01 02 04
EAR, NOSE & EYE CONTACT	01 02 04	PRODUCER/PROC	01 02 04
ENDOCRINE/IMMUNOL	01 02 04	MATERIAL	01 02 04
ENDOCRINE/IMMUNOL	01 02 04	OTHER	01 02 04
ENDOCRINE/IMMUNOL	01 02 04		
CONTAMINANT	01 02 04		
ALL INTO GLASS	01 02 04		
ALL INTO (ANIMAL)	01 02 04		
ALL INTO (HUMAN)	01 02 04		
METABOLISM/HANDLING (ANIMAL)	01 02 04		
METABOLISM/HANDLING (HUMAN)	01 02 04		
ACUT TOX (ANIMAL)	01 02 04		
ACUT TOX (HUMAN)	01 02 04		
CH. TOX (ANIMAL)	01 02 04		
CH. TOX (HUMAN)	01 02 04		
SUB ACUTE TOX (ANIMAL)	01 02 04		
SUB CHRONIC TOX (ANIMAL)	01 02 04		
CHRONIC TOX (ANIMAL)	01 02 04		
CHRONIC TOX (HUMAN)	01 02 04		

TESTS IN RELEVANCE

TESTS

TOXICOLOGICAL CHANGES

EXPOSURE:

heat transfer

fluid

water

water

water

water

water

water

water

water

water

Rats and dogs were exposed to dichlorofluoromethane vapors at exposures of 0, 0.1 and 0.5% ($\frac{1}{4}$ %) for 6 hours/day, 5 days/week, for 28 days. The high-dose dogs showed a slight decrease in body weight gain and mild liver effects. The water, water evidence by blood chemistry and microscopic changes (not specified). The NOAEL is 0.1%.